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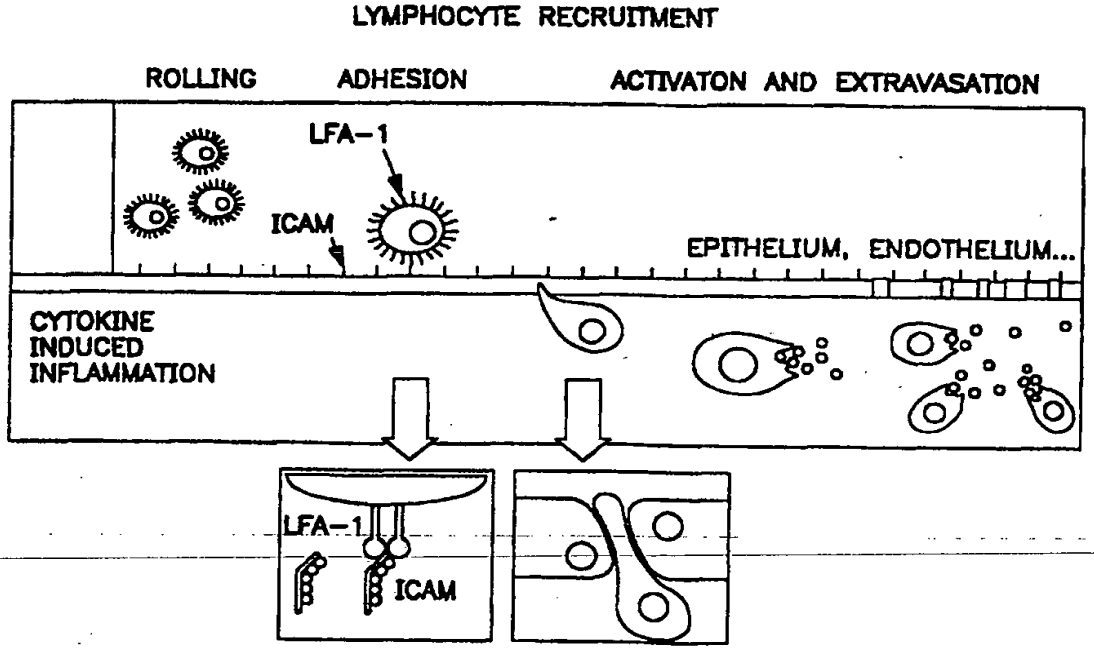

(57) Abstract

Compounds of the general structure D–L–B–(AA), for example (A), that are useful for treating Mac–1 or LFA–1–mediated disorders such as inflammatory disorders, allergies, and autoimmune diseases are provided.

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ANTAGONISTS FOR TREATMENT OF CD11/CD18 ADHESION RECEPTOR MEDIATED DISORDERS

Field of the Invention

This invention relates to methods and therapeutic compositions for treating mammals, preferably humans, who suffer from or are susceptible to (CD11/CD18) adhesion receptor mediated disorders, especially leukocyte LFA-1 mediated disorders. In particular, it relates to methods for ameliorating or modulating immune responses such as those caused by inflammation, autoimmune responses and host-graft rejection, as exemplified by psoriasis, rheumatoid arthritis, asthma, multiple sclerosis, rejection following transplanted grafts and the like.

Background of the Invention

Inflammation

Human peripheral blood is composed principally of red blood cells, platelets and white blood cells or leukocytes. The family of leukocytes are further classified as neutrophils, lymphocytes (mostly B- and T-cell subtypes), monocytes, eosinophils and basophils. Neutrophils, eosinophils and basophils are sometimes referred to as "granulocytes" or "polymorphonuclear (PMN) granulocytes" because of the appearance of granules in their cytoplasm and their multiple nuclei. Granulocytes and monocytes are often classified as "phagocytes" because of their ability to phagocytose or ingest micro-organisms and foreign mater referred to generally as "antigens". Monocytes are so called because of their large single nucleus and these cells may in turn become macrophages. Phagocytes are important in defending the host against a variety of infections and together with lymphocytes are also involved in inflammatory disorders. The neutrophil is the most common leukocyte found in human peripheral blood followed closely by the lymphocyte. In a microliter of normal human peripheral blood, there are about 6,000 leukocytes, of which about 4,000 are neutrophils, 1500 are lymphocytes, 250 are monocytes, 150 are eosinophils and 25 are basophils.

During an inflammatory response peripheral blood leukocytes are recruited to the site of inflammation or injury by a series of specific cellular interactions (see Fig. 1). The initiation and maintenance of immune functions are regulated by intercellular adhesive interactions as well as signal transduction resulting from interactions between leukocytes and other cells. Leukocyte adhesion to vascular endothelium and migration from the circulation to sites of inflammation is a critical step in the inflammatory response (Fig. 1). T-cell lymphocyte immune recognition requires the interaction of the T-cell receptor with antigen (in combination with the major histocompatibility complex) as well as adhesion receptors, which promote attachment of T-cells to antigen-presenting cells and transduce signals for T-cell activation. The lymphocyte function associated antigen-1 (LFA-1) has been identified as the major integrin that mediates lymphocyte adhesion and activation leading to a normal immune response, as well as several pathological states (Springer, T.A., *Nature* 346:425-434 (1990)). Intercellular adhesion molecules (ICAM) -1, -2, and -3, members of the immunoglobulin superfamily, are ligands for LFA-1 found on endothelium, leukocytes and other cell types. The binding of LFA-1 to ICAMs mediate a range of lymphocyte functions including

lymphokine production of helper T-cells in response to antigen presenting cells, T-lymphocyte mediated target cells lysis, natural killing of tumor cells, and immunoglobulin production through T-cell-B-cell interactions. Thus, many facets of lymphocyte function involve the interaction of the LFA-1 integrin and its ICAM ligands. These LFA-1:ICAM mediated interactions have been directly implicated in numerous inflammatory disease states including; graft rejection, dermatitis, psoriasis, asthma and rheumatoid arthritis.

While LFA-1 (CD11a/CD18) on lymphocytes plays a key role in chronic inflammation and immune responses, other members of the leukocyte integrin family (CD11b/CD18, CD11c/CD18 and CD11d/CD18) also play important roles on other leukocytes, such as granulocytes and monocytes, particularly in early response to infective agents and in acute inflammatory response.

The primary function of polymorphonuclear leukocytes, derived from the neutrophil, eosinophil and basophil lineage, is to sense inflammatory stimuli and to emigrate across the endothelial barrier and carry out scavenger function as a first line of host defense. The integrin Mac-1(CD11b/CD18) is rapidly upregulated on these cells upon activation and binding to its multiple ligands which results in the release of oxygen derived free radicals, protease's and phospholipases. In certain chronic inflammatory states this recruitment is improperly regulated resulting in significant cellular and tissue injury. (Harlan, J. M., *Acta Med Scand Suppl.*, 715:123 (1987); Weiss, S., *New England J. of Med.*, 320:365 (1989)).

LFA-1 (CD11a/CD18) and Mac-1 (CD11b/CD18)

The (CD11/CD18) family of adhesion receptor molecules comprises four highly related cell surface glycoproteins; LFA-l (CD11a/CD18), Mac-1 (CD11b/CD18), p150.95 (CD11c/CD18) and (CD11d/CD18). LFA-1 is present on the surface of all mature leukocytes except a subset of macrophages and is considered the major lymphoid integrin. The expression of Mac-1, p150.95 and CD11d/CD18 is predominantly confined to cells of the myeloid lineage (which include neutrophils, monocytes, macrophage and mast cells). Functional studies have suggested that LFA-1 interacts with several ligands, including ICAM-1 (Rothlein*et al.*, *J. Immunol.* 137:1270-1274 (1986), ICAM-2, (Staunton et al., *Nature* 339:361-364 (1989)), ICAM-3 (Fawcett et al., *Nature* 360:481-484 (1992); Vezeux et al., *Nature* 360:485-488, (1992); de Fougerolles and Springer, *J. Exp. Med.* 175:185-190 (1990)) and Telencephalin (Tian et al., *J. Immunol.* 158:928-936 (1997)).

The CD11/CD18 family is related structurally and genetically to the larger integrin family of receptors that modulate cell adhesive interactions, which include; embryogenesis, adhesion to extracellular substrates, and cell differentiation (Hynes, R. O., *Cell* 48:549-554 (1987); Kishimoto*et al.*, *Adv. Immunol.* 46:149-182 (1989); Kishimoto*et al.*, *Cell* 48:681-690 (1987); Ruoslahti*et al.*, *Science* 238:491-497 (1987).

Integrins are a class of membrane-spanning heterodimers comprising an α subunit in noncovalent association with a β subunit. The β subunits are generally capable of association with more than one α subunit and the heterodimers sharing a common β subunit have been classified as

subfamilies within the integrin population (Larson and Springer, "Structure and function of leukocyte integrins," *Immunol. Rev.* 114:181-217 (1990)).

The integrin molecules of the CD11/CD18 family, and their cellular ligands, have been found to mediate a variety of cell-cell interactions, especially in inflammation. These proteins have been demonstrated to be critical for adhesive functions in the immune system (Kishimoto*et al., Adv. Immunol.* 46:149-182 (1989)). Monoclonal antibodies to LFA-1 have been shown to block leukocyte adhesion to endothelial cells (Dustin *et al., J. Cell. Biol.* 107:321-331 (1988); Smith*et al., J. Clin. Invest.* 83:2008-2017 (1989)) and to inhibit T-cell activation (Kuypers et al., *Res. Immunol.*, 140:461 (1989)), conjugate formation required for antigen-specific CTL killing (Kishimoto*et al., Adv. Immunol.* 46:149-182 (1989)), T. cell proliferation (Davignon*et al., J. Immunol.* 127:590-595 (1981)) and NK cell killing (Krensky*et al., J. Immunol.* 131:611-616 (1983)).

ICAMs

ICAM-1 (CD54) is a cell surface adhesion receptor that is a member of the immunoglobulin protein super-family (Rothlein*et al., J. Immunol.* 137:1270-1274 (1986); Staunton*et al., Cell* 52:925-933 (1988). Members of this superfamily are characterized by the presence of one or more Ig homology regions, each consisting of a disulfide-bridged loop that has a number of anti-parallel β-pleated strands arranged in two sheets. Three types of homology regions have been identified, each with a typical length and having a consensus sequence of amino acid residues located between the cysteines of the disulfide bond (Williams, A. F. *et al. Ann Rev. Immunol.* 6:381-405 (1988); Hunkapillar, T. *et al. Adv. Immunol.* 44:1-63 (1989). ICAM-1 is expressed on a variety of hematopoietic and non-hematopoietic cells and is upregulated at sites of inflammation by a variety of inflammatory mediators (Dustin *et al., J. Immunol.*, 137:256-254 (1986)). ICAM-1 is a 90,000-110,000 M_r glycoprotein with a low messenger RNA levels and moderate surface expression on unstimulated endothelial cells. LPS, IL-1 and TNF strongly upregulate ICAM-1 mRNA and surface expression with peak expression at approximately 18-24 hours (Dustin*et al., J. Cell. Biol.* 107:321-331 (1988); Staunton*et al., Cell* 52:925-933 (1988)). ICAM-1 has five extracellular Ig like domains (designated Domains 1, 2, 3, 4 and 5 or D1, D2, D3, D4 and D5) and an intracellular or cytoplasmic domain. The structures and sequence of the domains is described by Staunton *et al.* (*Cell* 52:925-933 (1988)).

ICAM-1 was defined originally as a counter-receptor for LFA-1 (Springer *et al., Ann. Rev. Immunol,* 5:223-252 (1987); Marlin*Cell* 51:813-819 (1987); Simmons*et al., Nature* 331:624-627 (1988); Staunton*Nature* 339:61-64 (1989); Staunton*et al., Cell* 52:925-933 (1988)). The LFA-1/ICAM-1 interaction is known to be at least partially responsible for lymphocyte adhesion (Dustin*et al., J. Cell. Biol.* 107:321-331 (1988); Mentzer*et al., J. Cell. Physiol.* 126:285-290 (1986)), monocyte adhesion (Amaout*et al., J. Cell Physiol.* 137:305 (1988); Mentzer*et al., J. Cell. Physiol.* 130:410-415 (1987); te Velde*et al., Immunology* 61:261-267 (1987)), and neutrophil adhesion (Lo*et al., J. Immunol.* 143(10):3325-3329 (1989); Smith*et al., J. Clin. Invest.* 83:2008-2017 (1989)) to endothelial cells. Through the development of function blocking monoclonal antibodies to ICAM-1 additional ligands for LFA-

1 were identified, ICAM-2 and ICAM-3 (Simmons, *Cancer Surveys* 24, Cell Adhesion and Cancer, 1995) that mediate the adhesion of lymphocytes to other leukocytes as well as non-hematopoietic cells. Interactions of LFA-1 with ICAM-2 are thought to mediate natural killer cell activity (Helander *et al., Nature* 382:265-267 (1996)) and ICAM-3 binding is thought to play a role in lymphocyte activation and the initiation of the immune response (Simmons, ibid). The precise role of these ligands in normal and aberrant immune responses remains to be defined.

Disorders Mediated by T Lymphocytes

Function blocking monoclonal antibodies have shown that LFA-1 is important in T-lymphocyte-mediated killing, T-helper lymphocyte responses, natural killing, and antibody-dependent killing (Springer *et al., Ann. Rev. Immunol* 5:223-252 (1987)). Adhesion to the target cell as well as activation and signaling are steps that are blocked by antibodies against LFA-1.

Many disorders and diseases are mediated through T lymphocytes and treatment of these diseases have been addressed through many routes. Rheumatoid arthritis (RA) is one such disorder. Current therapy for RA includes bed rest, application of heat, and drugs. Salicylate is the currently preferred treatment drug, particularly as other alternatives such as immunosuppressive agents and adrenocorticosteroids can cause greater morbidity than the underlying disease itself. Nonsteroidal anti-inflammatory drugs are available, and many of them have effective analgesic, anti-pyretic and anti-inflammatory activity in RA patients. These include cyclosporin, indomethacin, phenylbutazone, phenylacetic acid derivatives such as ibuprofen and fenoprofen, naphthalene acetic acids (naproxen), pyrrolealkanoic acid (tometin), indoleacetic acids (sulindac), halogenated anthranilic acid (meclofenamate sodium), piroxicam, and diflunisal. Other drugs for use in RA include anti-malarials such as chloroquine, gold salts and penicillamine. These alternatives frequently produce severe side effects, including retinal lesions and kidney and bone marrow toxicity. Immunosuppressive agents such as methotrexate have been used only in the treatment of severe and unremitting RA because of their toxicity. Corticosteroids also are responsible for undesirable side effects (e.g., cataracts, osteoporosis, and Cushing's disease syndrome) and are not well tolerated in many RA patients.

Another disorder mediated by T lymphocytes is host rejection of grafts after transplantation. Attempts to prolong the survival of transplanted allografts and xenografts, or to prevent host versus graft rejection, both in experimental models and in medical practice, have centered mainly on the suppression of the immune apparatus of the host/recipient. This treatment has as its aim preventive immunosuppression and/or treatment of graft rejection. Examples of agents used for preventive immunosuppression include cytotoxic drugs, anti-metabolites, corticosteroids, and anti-lymphocytic serum. Nonspecific immunosuppressive agents found particularly effective in preventive immunosuppression (azathioprine, bromocryptine, methylprednisolone, prednisone, and most recently, cyclosporin A) have significantly improved the clinical success of transplantation. The nephrotoxicity of cyclosporin A after renal transplantation has been reduced by co-administration of steroids such as prednisolone, or

prednisolone in conjunction with azathioprine. In addition, kidneys have been grafted successfully using anti-lymphocyte globulin followed by cyclosporin A. Another protocol being evaluated is total lymphoid irradiation of the recipient prior to transplantation followed by minimal immunosuppression after transplantation.

Treatment of rejection has involved use of steroids, 2-amino-6-aryl-5-substituted pyrimidines, heterologous anti-lymphocyte globulin, and monoclonal antibodies to various leukocyte populations, including OKT-3. See generally *J. Pediatrics*, 111: 1004-1007 (1987), and specifically U.S. Pat. No. 4,665,077.

The principal complication of immunosuppressive drugs is infections. Additionally, systemic immunosuppression is accompanied by undesirable toxic effects (e.g., nephrotoxicity when cyclosporin A is used after renal transplantation) and reduction in the level of the hemopoietic stem cells. Immunosuppressive drugs may also lead to obesity, poor wound healing, steroid hyperglycemia, steroid psychosis, leukopenia, gastrointestinal bleeding, lymphoma, and hypertension.

In view of these complications, transplantation immunologists have sought methods for suppressing immune responsiveness in an antigen-specific manner (so that only the response to the donor alloantigen would be lost). In addition, physicians specializing in autoimmune disease strive for methods to suppress autoimmune responsiveness so that only the response to the self-antigen is lost. Such specific immunosuppression generally has been achieved by modifying either the antigenicity of the tissue to be grafted or the specific cells capable of mediating rejection. In certain instances, whether immunity or tolerance will be induced depends on the manner in which the antigen is presented to the immune system. Pretreating the allograft tissues by growth in tissue culture before transplantation has been found in two murine model systems to lead to permanent acceptance across MHC barriers. Lafferty *et al., Transplantation*, 22:138-149 (1976); Bowen *et al., Lancet*, 2:585-586 (1979). It has been hypothesized that such treatment results in the depletion of passenger lymphoid cells and thus the absence of a stimulator cell population necessary for tissue immunogenicity. Lafferty *et al., Annu. Rev. Immunol.*, 1:143 (1983). See also Lafferty *et al., Science*, 188:259-261 (1975) (thyroid held in organ culture), and Gores *et al., J. Immunol.*, 137:1482-1485 (1986) and Faustman *et al., Proc. Natl. Acad. Sci. U.S.A.*, 78: 5156-5159 (1981) (islet cells treated with murine anti-Ia antisera and complement before transplantation). Also, thyroids taken from donor animals pretreated with lymphocytotoxic drugs and gamma radiation and cultured for ten days *in vitro* were not rejected by any normal allogeneic recipient (Gose and Bach, *J.Exp.Med.*, 149:1254-1259 (1979)). All of these techniques involve depletion or removal of donor lymphocyte cells.

In some models such as vascular and kidney grafts, there exists a correlation between Class II matching and prolonged allograft survival, a correlation not present in skin grafts (Pescovitz *et al., J.Exp.Med.*, 160:1495-1508 (1984); Conti *et al., Transplant. Proc.*, 19: 652-654 (1987)). Therefore, donor-recipient HLA matching has been utilized. Additionally, blood transfusions

prior to transplantation have been found to be effective (Opelz *et al., Transplant. Proc.*, 4: 253 (1973); Persijn *et al., Transplant. Proc.*, 23:396 (1979)). The combination of blood transfusion before transplantation, donor-recipient HLA matching, and immunosuppression therapy (cyclosporin A) after transplantation was found to improve significantly the rate of graft survival, and the effects were found to be additive (Opelz *et al., Transplant. Proc.*, 17:2179 (1985)).

The transplantation response may also be modified by antibodies directed at immune receptors for MHC antigens (Bluestone *et al., Immunol. Rev.* 90:5-27 (1986)). Further, graft survival can be prolonged in the presence of antigraft antibodies, which lead to a host reaction that in turn produces specific immunosuppression (Lancaster *et al., Nature*, 315: 336-337 (1985)). The immune response of the host to MHC antigens may be modified specifically by using bone marrow transplantation as a preparative procedure for organ grafting. Thus, anti-T-cell monoclonal antibodies are used to deplete mature T-cells from the donor marrow inoculum to allow bone marrow transplantation without incurring graft-versus-host disease (Mueller-Ruchholtz *et al., Transplant Proc.*, 8:537-541 (1976)). In addition, elements of the host's lymphoid cells that remain for bone marrow transplantation solve the problem of immunoincompetence occurring when fully allogeneic transplants are used.

As shown in Fig. 1, lymphocyte adherence to endothelium is a key event in the process of inflammation. There are at least three known pathways of lymphocyte adherence to endothelium, depending on the activation state of the T-cell and the endothelial cell. T-cell immune recognition requires the contribution of the T-cell receptor as well as adhesion receptors, which promote attachment of - cells to antigen-presenting cells and transduce regulatory signals for T-cell activation. The lymphocyte function associated (LFA) antigen-1 (LFA-1, CD11a/CD18, $\alpha_L\beta_2$: where α_L is CD11a and β_2 is CD18) has been identified as the major integrin receptor on lymphocytes involved in these cell adherence interactions leading to several pathological states. ICAM-1, the endothelial cell immunoglobulin-like adhesion molecule, is a known ligand for LFA-1 and is implicated directly in graft rejection, psoriasis, and arthritis.

LFA-1 is required for a range of leukocyte functions, including lymphokine production of helper T-cells in response to antigen-presenting cells, killer T-cell-mediated target cell lysis, and immunoglobulin production through T-cell/B-cell interactions. Activation of antigen receptors on T-cells and B-cells allows LFA-1 to bind its ligand with higher affinity.

Monoclonal antibodies (MAbs) directed against LFA-1 led to the initial identification and investigation of the function of LFA-1 (Davignon *et al., J. Immunol.*, 127:590 (1981)). LFA-1 is present only on leukocytes (Krenskey *et al., J. Immunol.*, 131:611 (1983)), and ICAM-1 is distributed on activated leukocytes, dermal fibroblasts, and endothelium (Dustin *et al., J. Immunol.* 137:245 (1986)).

Previous studies have investigated the effects of anti-CD11a MAbs on many T-cell-dependent immune functions *in vitro* and a limited number of immune responses *in vivo*. *In vitro*, anti-CD11a MAbs inhibit T-cell activation (Kuypers *et al., Res. Immunol.*, 140:461 (1989)), T-cell-

dependent B-cell proliferation and differentiation (Davignon *et al., supra*; Fischer *et al., J. Immunol.*, 136:3198 (1986)), target cell lysis by cytotoxic T-lymphocytes (Krensky *et al., supra*), formation of immune conjugates (Sanders *et al., J. Immunol.*, 137:2395 (1986); Mentzer *et al., J. Immunol.*, 135:9 (1985)), and the adhesion of T-cells to vascular endothelium (Lo *et al., J. Immunol.*, 143:3325 (1989)). Also, the antibody 5C6 directed against CD11b/CD18 was found to prevent intra-islet infiltration by both macrophages and T cells and to inhibit development of insulin-dependent diabetes mellitis in mice (Hutchings *et al., Nature*, 348: 639 (1990)).

The observation that LFA-1:ICAM-1 interaction is necessary to optimize T-cell function *in vitro*, and that anti-CD11a MAbs induce tolerance to protein antigens (Benjamin *et al., Eur. J. Immunol.*, 18:1079 (1988)) and prolongs tumor graft survival in mice (Heagy *et al., Transplantation*, 37: 520-523 (1984)) was the basis for testing the MAbs to these molecules for prevention of graft rejection in humans.

Experiments have also been carried out in primates. For example, based on experiments in monkeys it has been suggested that a MAb directed against ICAM-1 can prevent or even reverse kidney graft rejection (Cosimi *et al.*, "Immunosuppression of Cynomolgus Recipients of Renal Allografts by R6.5, a Monoclonal Antibody to Intercellular Adhesion Molecule-1," in Springer *et al.* (eds.), *Leukocyte Adhesion Molecules* New York: Springer, (1988), p. 274; Cosimi *et al., J. Immunology*, 144:4604-4612 (1990)). Furthermore, the *in vivo* administration of anti-CD11a MAb to cynomolgus monkeys prolonged skin allograft survival (Berlin *et al., Transplantation*, 53: 840-849 (1992)).

The first successful use of a rat anti-murine CD11a antibody (25-3; IgG1) in children with inherited disease to prevent the rejection of bone-marrow-mismatched haploidentical grafts was reported by Fischer *et al., Lancet*, 2: 1058 (1986). Minimal side effects were observed. See also Fischer *et al., Blood*, 77: 249 (1991); van Dijken *et al., Transplantation*, 49:882 (1990); and Perez *et al., Bone Marrow Transplantation*, 4:379 (1989). Furthermore, the antibody 25-3 was effective in controlling steroid-resistant acute graft-versus-host disease in humans (Stoppa *et al., Transplant. Int.*, 4:3-7 (1991)).

However, these results were not reproducible in leukemic adult grafting with this MAb (Maraninchi *et al., Bone Marrow Transplant*, 4:147-150 (1989)), or with an anti-CD18 MAb, directed against the invariant chain of LFA-1, in another pilot study (Baume *et al., Transplantation*, 47: 472 (1989)). Furthermore, a rat anti-murine CD11a MAb, 25-3, was unable to control the course of acute rejection in human kidney transplantation (LeMauff *et al., Transplantation*, 52: 291 (1991)).

A review of the use of monoclonal antibodies in human transplantation is provided by Dantal and Soulillou, *Current Opinion in Immunology*, 3:740-747 (1991).

An earlier report showed that brief treatment with either anti-LFA-1 or anti-ICAM-1 MAbs minimally prolonged the survival of primarily vascularized heterotopic heart allografts in mice (Isobe *et al., Science*, 255:1125 (1992)). However, combined treatment with both MAbs was required to achieve long-term graft survival in this model.

Independently, it was shown that treatment with anti-LFA-1 MAb alone potently and effectively prolongs the survival of heterotopic (ear-pinnae) nonprimarily vascularized mouse heart grafts using a maximum dose of 4 mg/kg/day and treatment once a week after a daily dose (Nakakura *et al., J. Heart Lung Transplant.,* 11:223 (1992)). Nonprimarily vascularized heart allografts are more immunogenic and more resistant to prolongation of survival by MAbs than primarily vascularized heart allografts (Warren *et al., Transplant. Proc.,* 5:717 (1973); Trager *et al., Transplantation,* 47:587 (1989)). The latter reference discusses treatment with L3T4 antibodies using a high initial dose and a lower subsequent dose.

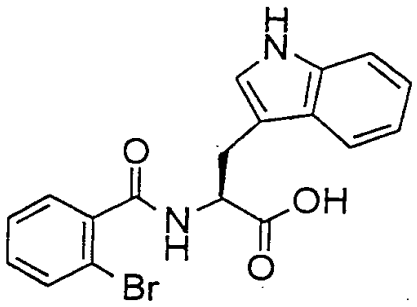
Another study on treating a sclerosis-type disease in rodents using similar antibodies to those used by Nakakura *et al., supra,* is reported by Yednock *et al., Nature,* 356:63-66 (1992).

Additional disclosures on the use of anti-LFA-1 antibodies and ICAM-1, ICAM-2, and ICAM-3 and their antibodies to treat LFA-1-mediated disorders include WO 91/18011 published 11/28/91, WO 91/16928 published 11/14/91, WO 91/16927 published 11/14/91, Can. Pat. Appln. 2,008,368 published 6/13/91, WO 90/03400, WO 90/15076 published 12/13/90, WO 90/10652 published 9/20/90, EP 387,668 published 9/19/90, WO 90/08187 published 7/26/90, WO 90/13281, WO 90/13316, WO 90/13281, WO 93/06864, WO 93/21953, WO 93/13210, WO 94/11400, EP 379,904 published 8/1/90, EP 346,078 published 12/13/89, U.S. Pat. No. 5,002,869, U.S. Pat. No. 5,071,964, U.S. Pat. No. 5,209,928, U.S. Pat. No. 5,223,396, U.S. Pat. No. 5,235,049, U.S. Pat. No. 5,284,931, U.S. Pat. No. 5,288,854, U.S. Pat. No. 5,354,659, Australian Pat. Appln. 15518/88 published 11/10/88, EP 289,949 published 11/9/88, and EP 303,692 published 2/22/89, EP 365,837, EP 314,863, EP 319,815, EP 468, 257, EP 362,526, EP 362, 531, EP 438,310.

Other disclosures on the use of LFA-1 and ICAM peptide fragments and antagonists include; U.S. Pat. No. 5,149,780, U.S. Pat. No. 5,288,854, U.S. Pat. No. 5,340,800, U.S. Pat. No. 5,424,399, U.S. Pat. No. 5,470,953, WO 90/03400, WO 90/13316, WO 90/10652, WO 91/19511, WO 92/03473, WO 94/11400, WO 95/28170, JP 4193895, EP 314,863, EP 362,526 and EP 362,531.

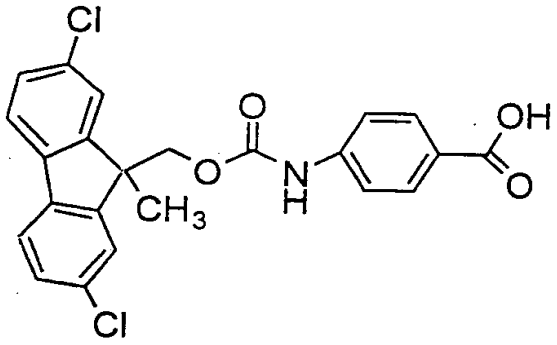
The above methods successfully utilizing anti-LFA-1 or anti-ICAM-1 antibodies, LFA-1 or ICAM-1 peptides, fragments or peptide antagonists represent an improvement over traditional immunosuppressive drug therapy. These studies demonstrate that LFA-1 and ICAM-1 are appropriate targets for antagonism. There is a need in the art to better treat disorders that are mediated by LFA-1 including autoimmune diseases, graft vs. host or host vs. graft rejection, and T-cell inflammatory responses, so as to minimize side effects and sustain specific tolerance to self- or xenoantigens. There is also a need in the art to provide a non-peptide or peptidomimetic antagonist to the LFA-1: ICAM-1 interaction.

At least one peptidomimetic antagonist of the LFA-1:ICAM-1 interaction has shown promise in various *in vitro* assays.



2-Bromobenzoyltryptophan exhibits IC_{50}'s of about 2μM and 10μM respectively in human LFA-1:ICAM-1 receptor binding and human T-cell adhesion assays described herein.

Recently, aminobenzoic acid derivatives of fluorene have been described in U.S. Patent 5,472,973 is useful anti-inflammatory agents. A representative compound is:



Objects of the Invention

Accordingly, it is an object of this invention to provide compositions and therapeutic methods for modulating adhesion between intracellular adhesion molecules (e.g. ICAM-1, -2 and -3) and the leukocyte integrin family of receptors.

It is an object to antagonize CD11/CD18 receptors associated with leukocytes, especially Mac-1 and LFA-1-mediated disorders with minimal side effects.

It is an object to control inappropriate inflammatory responses and prevent damage to healthy tissue.

More specifically, it is an object to treat LFA-1-mediated disorders including: psoriasis; responses associated with inflammatory bowel disease (such as Crohn's disease and ulcerative colitis), dermatitis, meningitis, encephalitis, uveitis, allergic conditions such as eczema and asthma, conditions involving infiltration of T-cells and chronic inflammatory responses, skin hypersensitivity reactions (including poison ivy and poison oak); atherosclerosis, autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus (SLE), diabetes mellitus, multiple sclerosis, Reynaud's syndrome, autoimmune thyroiditis, experimental autoimmune encephalomyelitis, Sjorgen's syndrome, juvenile onset diabetes, and immune responses associated with delayed hypersensitivity mediated by cytokines and T-lymphocytes typically found in

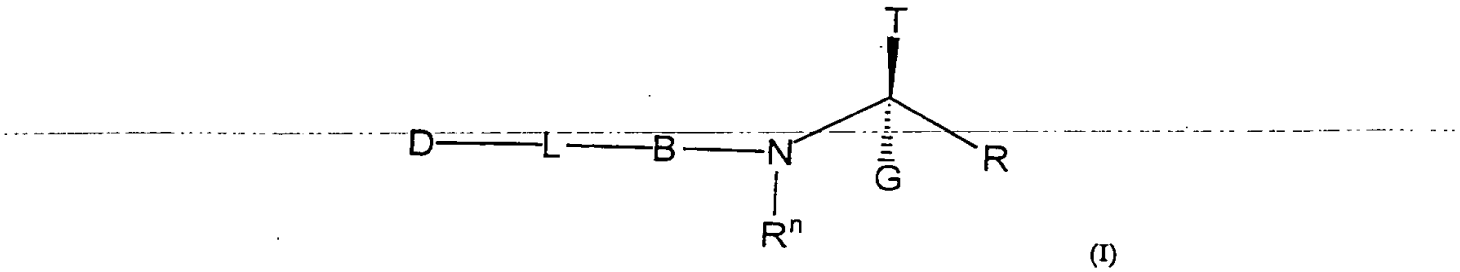
tuberculosis, sarcoidosis, polymyositis, granulomatosis and vasculitis; pernicious anemia; diseases involving leukocyte diapedesis; CNS inflammatory disorder, multiple organ injury syndrome secondary to septicaemia or trauma; autoimmune hemolytic anemia; myasthemia gravis; antigen-antibody complex mediated diseases; all types of transplantations, including graft vs. host or host vs. graft disease, HIV and rhinovirus infection, pulmonary fibrosis, and the like.

These and other objects will become apparent to one of ordinary skill in the art.

Summary of the Invention

These objects are accomplished by providing a method and antagonist compositions for modulating adhesion between intracellular adhesion molecules (e.g. ICAM-1, -2 and -3) and the leukocyte integrin family of receptors. The method and antagonists are especially useful for treating CD11/CD18, especially Mac-1 and LFA-1-mediated disorders in a mammal, especially a human, comprising administering to the mammal a therapeutically effective amount of the antagonist. Suitable leukocyte integrin antagonists, especially Mac-1 and LFA-1 antagonists of this invention are represented by Structural Formula I below. Preferably, the LFA-1 antagonist is a specific antagonist of the leukocyte integrin CD11a(α_L)/CD18(β_2). Such antagonists are especially useful to treat chronic LFA-1 mediated disorders. Preferably, these LFA-1 antagonists are used to treat: psoriasis, alopecia, organ transplant, inflammatory bowel disease (IBD), rheumatoid arthritis (RA), systemic lupus erythematosis (SLE), type-1 diabetes, multiple sclerosis (MS), asthma, graft verses host (GVH) disease, scleredoma, endometriosus and vitiligo. Optionally, certain compounds embraced by Formula I are also capable of antagonizing Mac-1 CD11b(α_M)/CD18(β_2) binding to ICAM-1 and additional ligands including iC3b, fibrinogen and Factor X. These compounds are therefore useful for inhibiting adhesion of neutrophils and leukocytes expressing both or either LFA-1 and Mac-1 in both chronic and acute leukocyte/neutrophil mediated disorders. More specifically these disorders include; ischemic reperfusion injury mediated by neutrophils such as acute myocardial infarction, restenosis following PTCA, invasive procedures such as cardiopulmanary bypass surgery, cerebral edema, stroke, traumatic brain injury, multiple sclerosis, systemic lupus erythematosis, hemorragic shock, burns, ischemic kidney disease, multi-organ failure, wound healing and scar formation, atherosclerosis as well as organ failure post-transplant.

The antagonist is represented by formula I

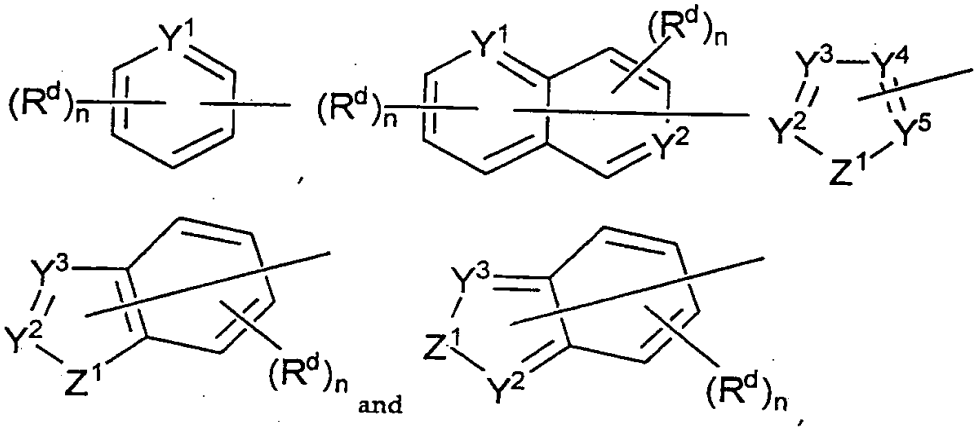


(I)

Where D is a mono-, bi-, or tricyclic saturated, unsaturated, or aromatic ring, each ring

having 5-, 6- or 7 atoms in the ring where the atoms in the ring are carbon or from1-4 heteroatoms selected from; nitrogen, oxygen, and sulfur, where any sulfur ring atom may optionally be oxidized and any carbon ring atom may form a double bond with O, NR^n and $CR^1R^{1'}$, each ring nitrogen substituted with R^n and any ring carbon substituted with R^d.

Optionally, D is an aromatic homocycle or aromatic heterocycle containing 1-3 heteroatoms selected from the group N, S and O, the homo- or hetero-cycles selected from:

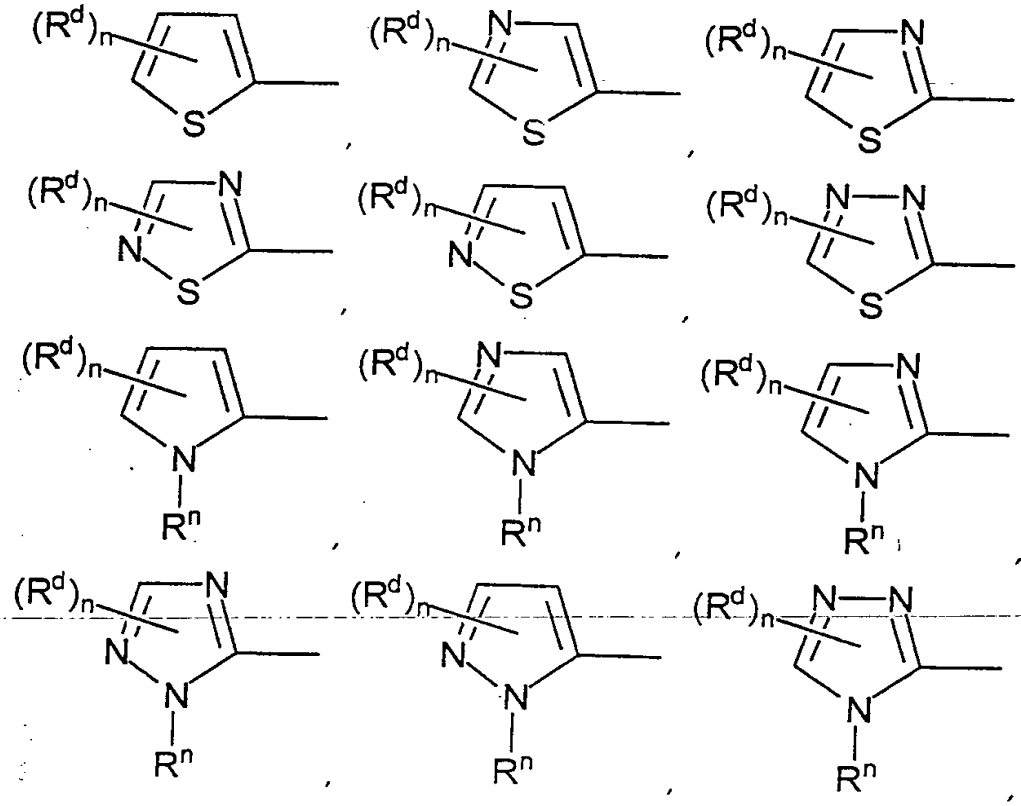


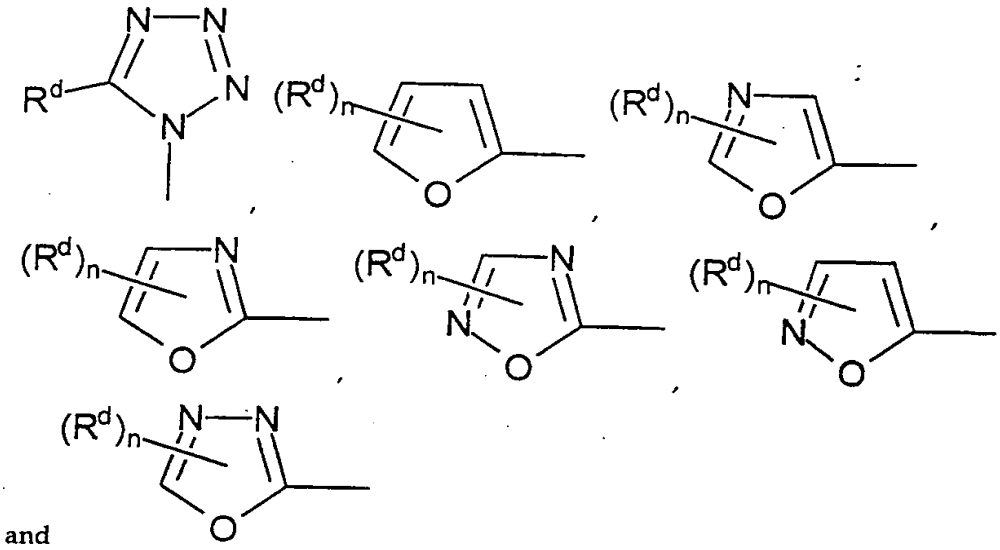
and

where Y^1, Y^2, Y^3, Y^4 and Y^5 are CH, CR^d or N, Z^1 is O, S, NH or NR^n and n is 0-3.

More specifically, D may be:

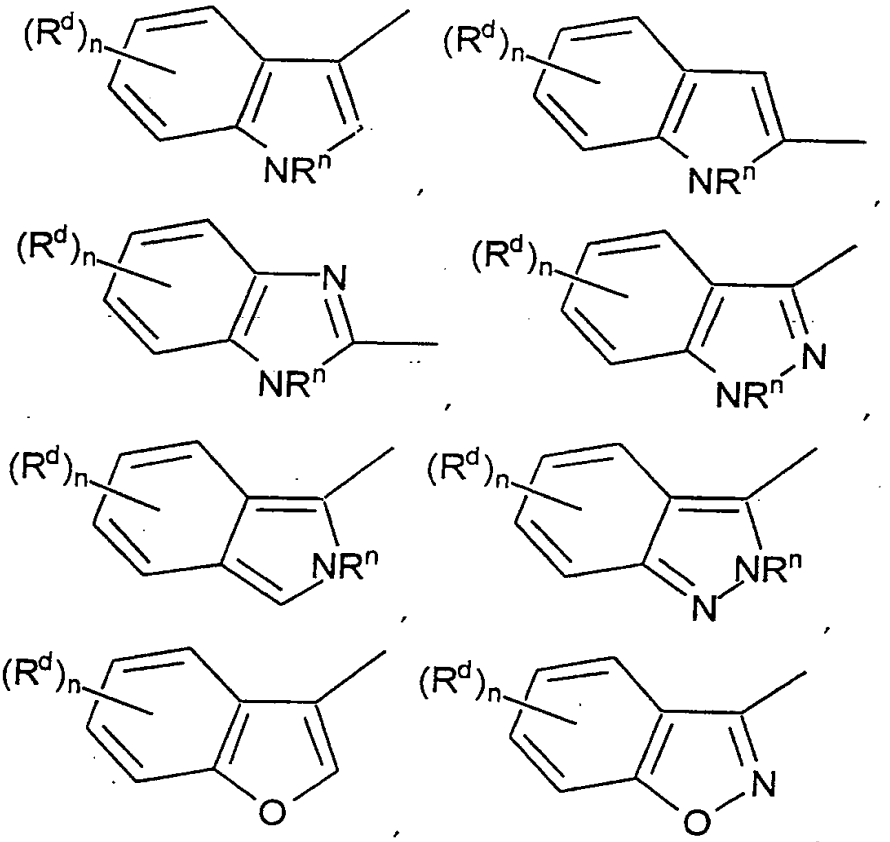
1) a 5-member aromatic heterocycle or het selected from;

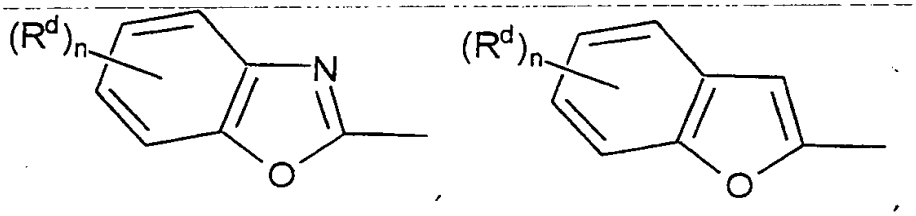


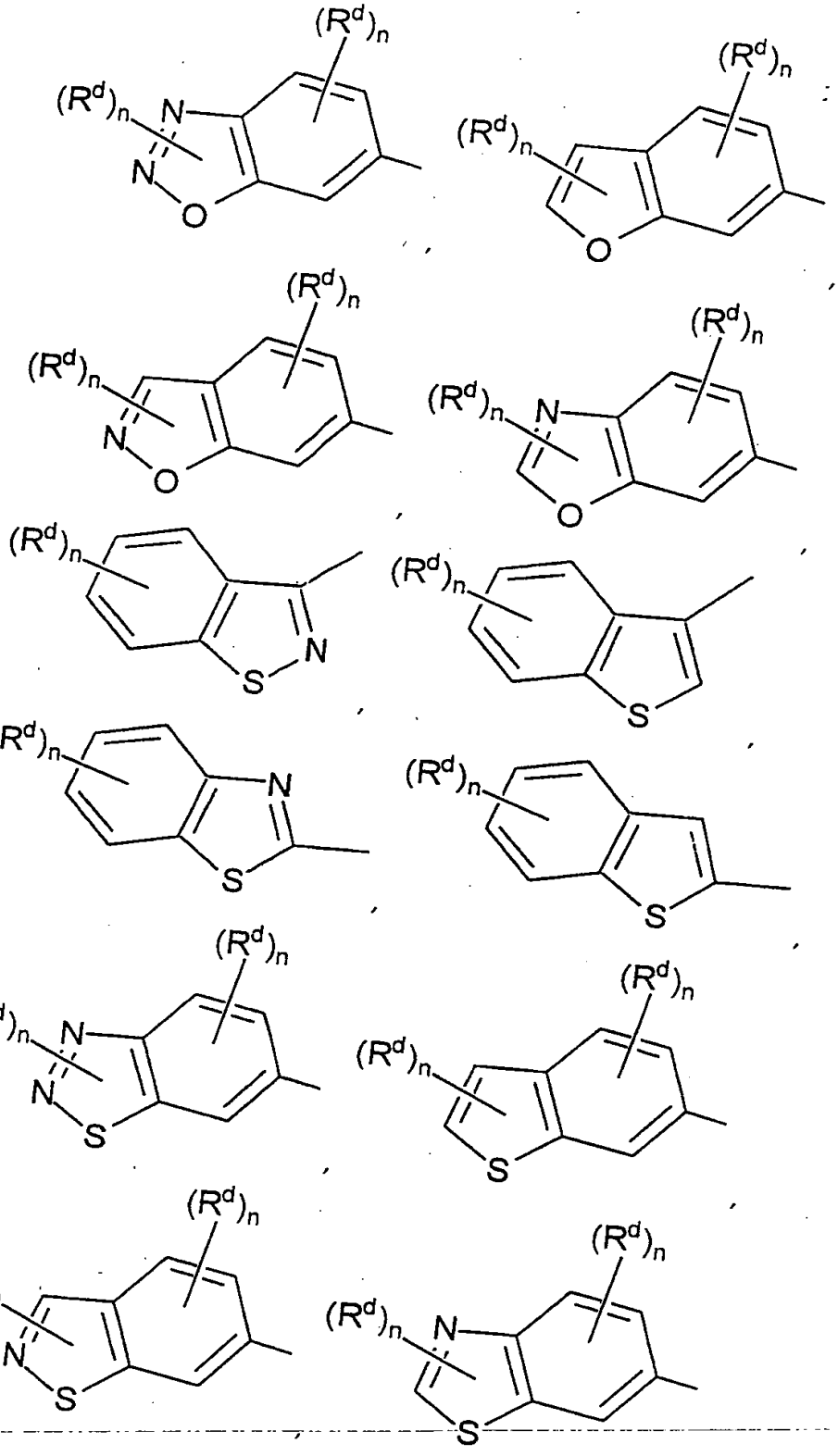


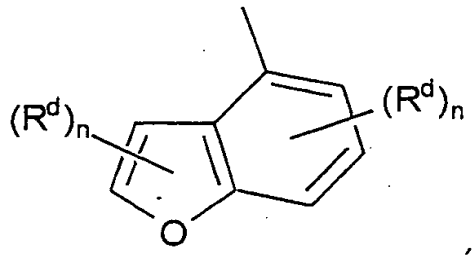
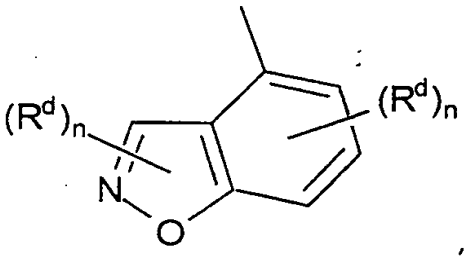
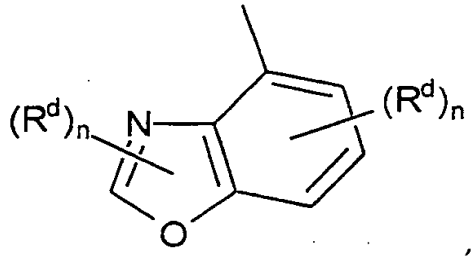
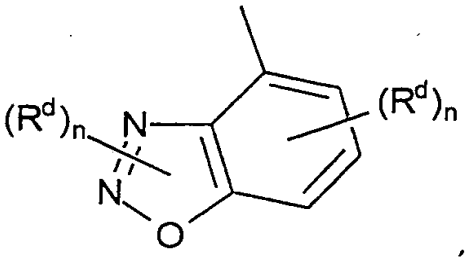
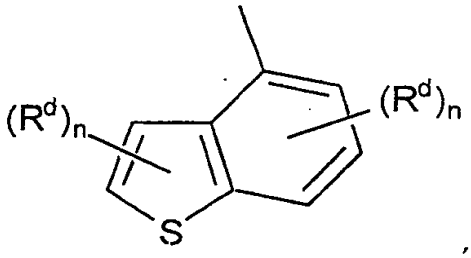
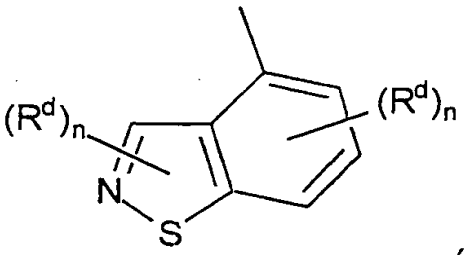
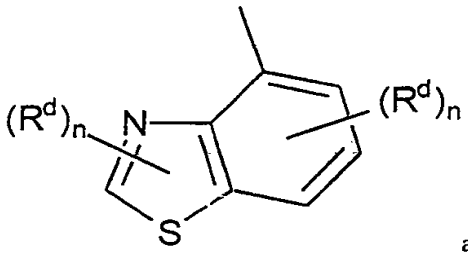
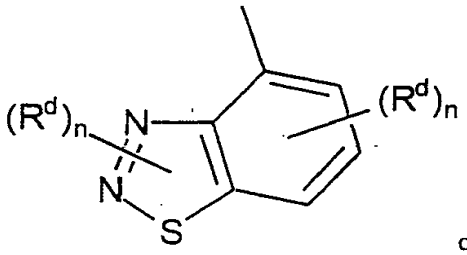
and

2) a 9-member aromatic heterobicycle selected from;



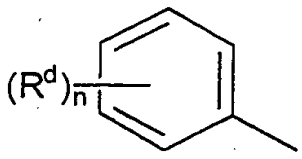
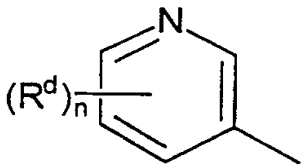
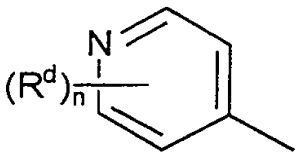
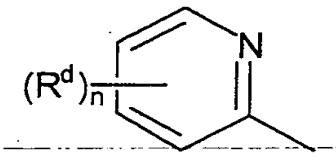




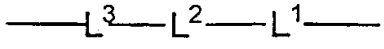
and or

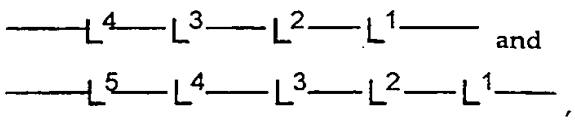
3) a 6-member aromatic hetero- or homocycle selected from;

and ;

L is a bivalent linking group selected from





where:

L^1 may be oxo (O), $S(O)_s$, C(=O), C(=N-R^n), C(=C$R^1R^{1'}$), C($R^1R^{1'}$), C(R^1), C, het, N(R^n) or N;

L^2 may be oxo (O), $S(O)_s$, C(=O), C(=N-O-R^o), C(=C$R^2R^{2'}$), C($R^2R^{2'}$), C(R^2), C, het, N(R^n) or N;

L^3 may be oxo (O), $S(O)_s$, C(=O), C(=N-O-R^o), C(=C$R^3R^{3'}$), C($R^3R^{3'}$) C(R^3), C, het, N(R^n) or N;

L^4 is absent or may be oxo (O), $S(O)_s$, C(=O), C(=N-O-R^o), C(=C$R^4R^{4'}$), C($R^4R^{4'}$), C(R^4), C, NR^n or N; and

L^5 is absent or may be oxo (O), $S(O)_s$, C(=O), C(=N-R^n), C($R^5R^{5'}$), C(=C$R^5R^{5'}$), C(R^5), C, NR^n or N;

provided that only one of L^1-L^3 may be het and that when one of L^1- L^3 is het the other L^1-L^5 may be absent.

R^1, $R^{1'}$, R^2, $R^{2'}$, R^3, $R^{3'}$, R^4, $R^{4'}$, R^5 and $R^{5'}$ each are independently selected from R^a, R^c and U-Q-V-W. Optionally, R^2 and $R^{2'}$ separately or together may form a saturated, unsaturated or aromatic fused ring with B through a substituent R^p on B, the fused ring containing 5, 6 or 7 atoms in the ring and optionally containing 1-3 heteroatoms selected from the group O, S and N. where any S or N may optionally be oxidized. Optionally, R^3 and $R^{3'}$ separately or together and R^4 and $R^{4'}$ separately or together may form a saturated, unsaturated or aromatic fused ring with D through a substituent R^d on D, the fused ring containing 5, 6 or 7 atoms in the ring and optionally containing 1-3 heteroatoms selected from the group O, S and N, where any S or N may optionally be oxidized. Also optionally, each R^1-R^5, or NR^n together with any other R^1- R^5 or NR^n may form a 5, 6 or 7 member homo- or heterocycle either saturated, unsaturated or aromatic optionally containing 1-3 additional heteroatoms selected from N, O and S, each cycle substituted with 0-3 R^d, where s is 0-2, and where any carbon or sulfur ring atom may optionally be oxidized.

More specifically, the bivalent linker L may be:

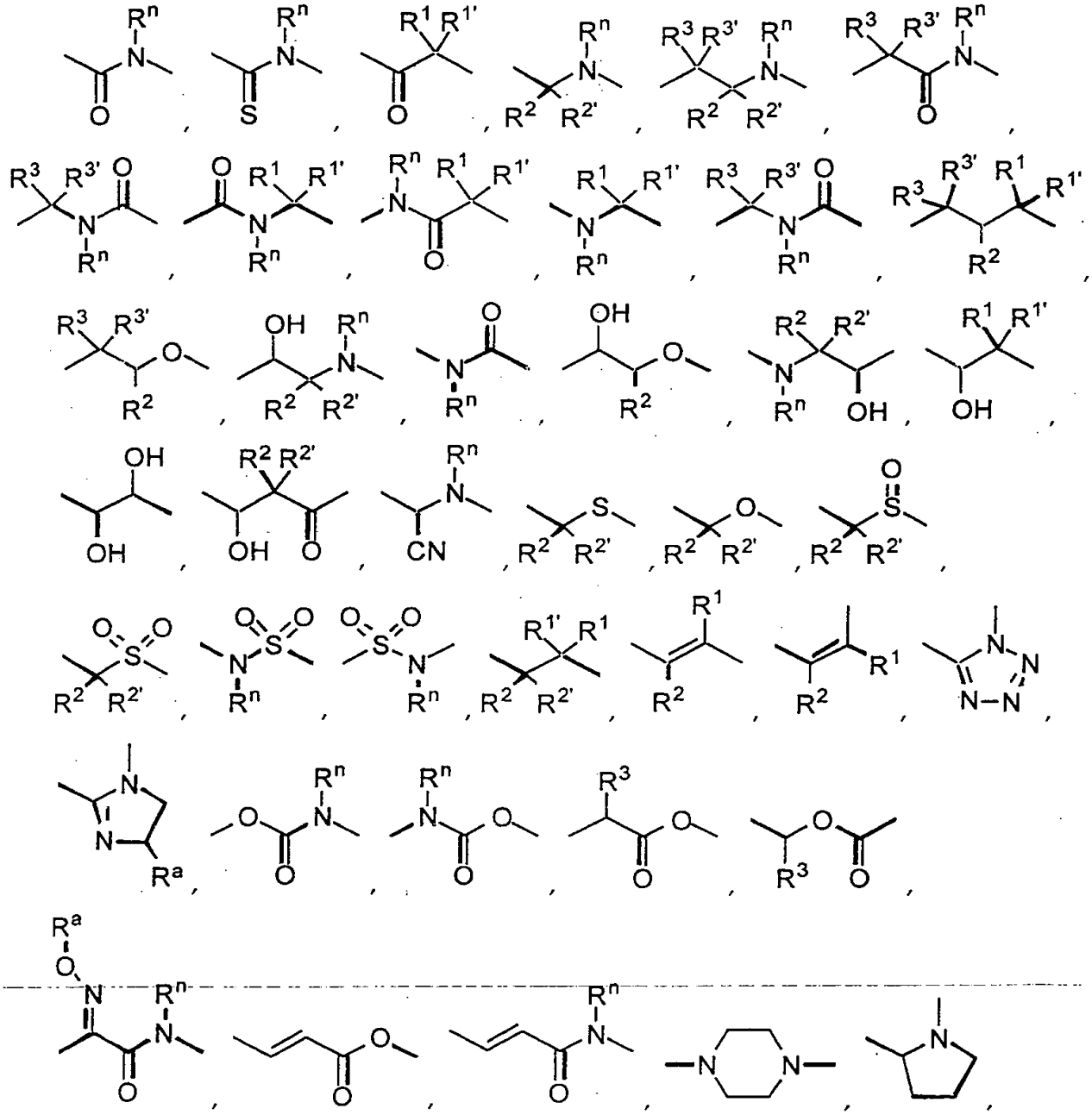
$-(CR^6R^{6'})_o$-Ai-$(CR^8R^{8'})_p$-,

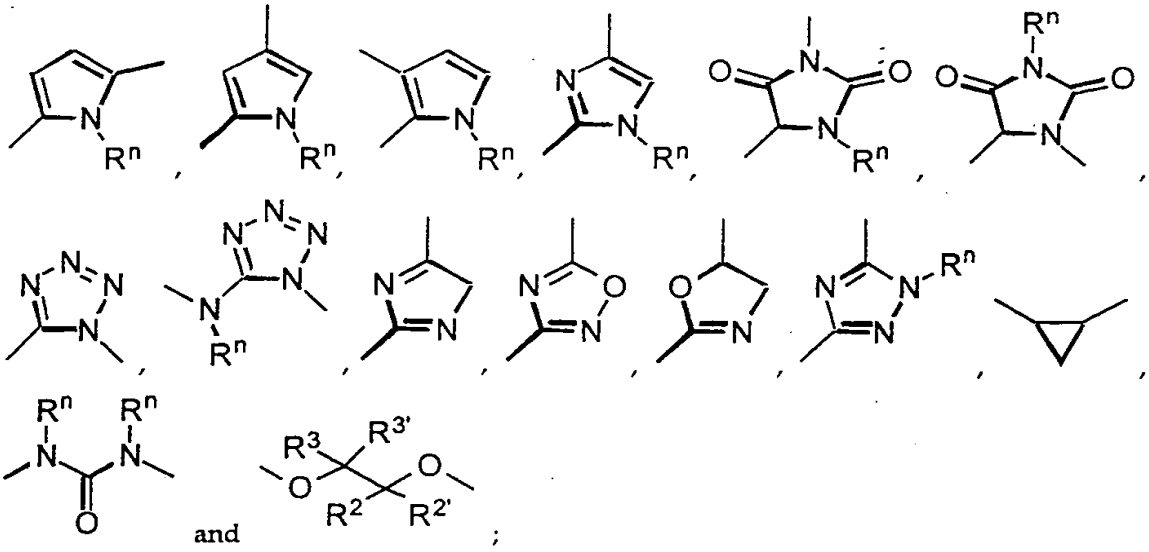
$-(CR^6R^{6'})_o$-het-$(CR^8R^{8'})_p$-,

$-(CR^6=CR^7)_q$-Ai-$(CR^8R^{8'})_p$- and

$-(CR^6R^{6'})_o$-Ai-$(CR^8=CR^9)_r$-,

where Ai is selected from



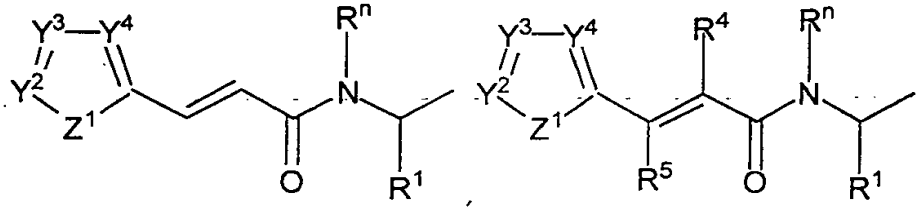


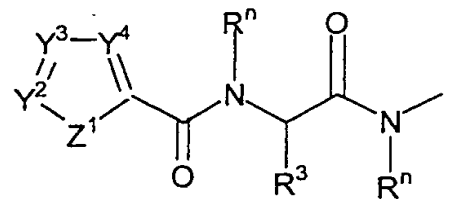
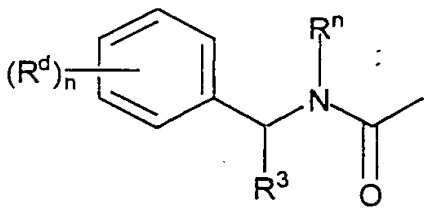
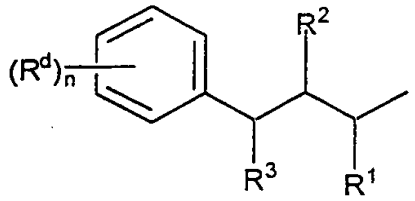
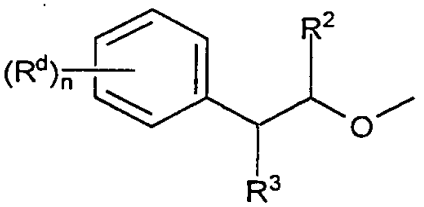
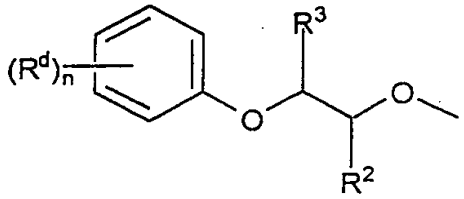
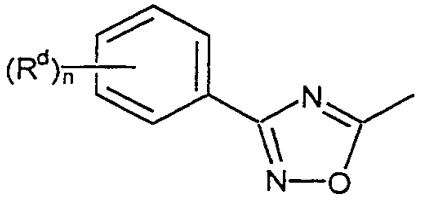
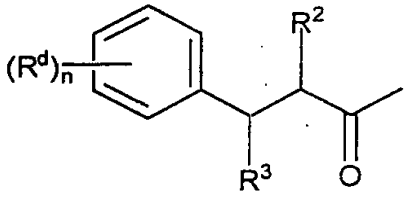
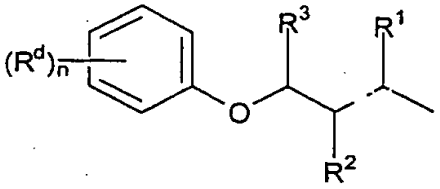
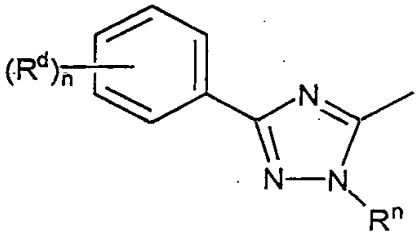
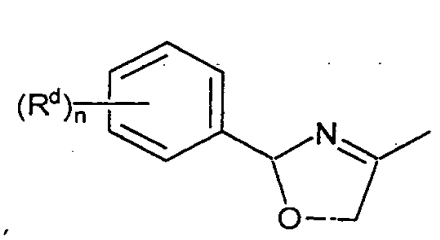
where o is 0-1, p is 0-1, q is 0-1 and r is 0-1.

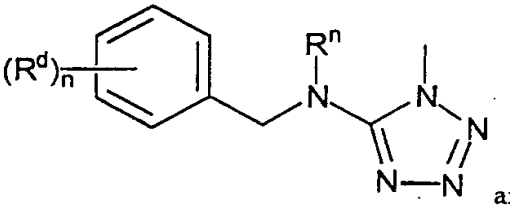
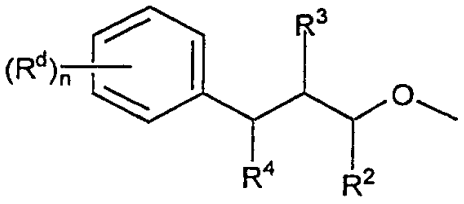
het is any mono-, bi-, or tricyclic saturated, unsaturated, or aromatic ring where at least one ring is a 5-, 6- or 7-membered ring containing from one to four heteroatoms selected from the group nitrogen, oxygen, and sulfur, the 5-membered ring having from 0 to 2 double bonds and the 6- or 7-membered ring having from 0 to 3 double bonds and where any carbon or sulfur atoms in the ring may optionally be oxidized, and where any nitrogen heteroatom may optionally be quaternized and where any ring may contain from 0-3 R^d.

Optionally L is a bivalent linking group selected from the group:
-C_3-C_5-alkyl-, -C_3-C_5-alkenyl-, -CH_2C(=O)NH-, -CH_2NH-C(=O)-, -O-CH_2-C(=O)-, -CH_2-CH_2-C(=O)-, -CH=CH-C(=O)NH-CH_2-, -CH=CH-C(=O)NH-CH-(CH_3)-, -CH(OH)-CH_2-O-, -CH(OH)-CH_2-N(CH_3)-, -CH(OH)-CH_2-CH_2-, -CH_2-CH_2-CH(OH)-, -O-CH_2-CH(OH)-, -O-CH_2-CH(OH)-CH_2-, -O-CH_2-CH_2-CH(OH)-, -O-CH_2-CH_2-O-, -CH_2-CH_2-CH_2-O-, -CH_2-CH(OH)-CH_2-O-, -CH_2-CH_2-O-, -CH-(CH_3)-NH-C(=O)-, -CH_2-NH-SO_2-, -NH-SO_2-CH_2-, -CH_2-SO_2NH-, -SO_2NH-CH_2-, -C(=O)-NH-C(=O)-, -NH-C(=O)-NH-, -NH-C(=O)-NH-CH_2-, -CH_2-NH-C(=O)-NH-, -C(=O)-NH-CH_2-C(=O)-NH -, -NH-C(=O)-O- and -O-C(=O)-NH-.

Optionally, specific D-L combinations are selected from:

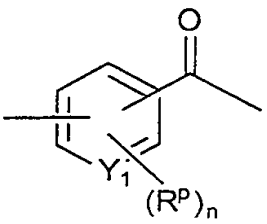
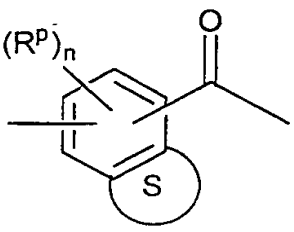


and

B is selected from the group

and

where

is a fused hetero- or homocyclic ring containing 5, 6 or 7 atoms, the ring being unsaturated, partially saturated or aromatic, the heteroatoms selected from 1-3 O, S and N.

Y_1 is selected from CH and N and n is 0-3.

G is selected from hydrogen and C_1-C_6alkyl, optionally G taken together with T may form a C_3-C_6cycloalkyl optionally substituted with -V-W.

T is selected from the group 1) a naturally occurring α-amino-acid side chain or derivatives thereto and U-Q-V-W.

U is an optionally substituted bivalent radical selected from the group;

C_1-C_6alkyl, C_0-C_6alkyl-Q, C_2-C_6alkenyl-Q, and C_2-C_6alkynyl-Q, where the substituents on any alkyl, alkenyl or alkynyl are 1-3 R^a.

Q is absent or is selected from the group; -O-, -S(O)$_s$-, -SO$_2$-N(R^n)-, -N(R^n)-, -N(R^n)-C(=O)-, -N(R^n)-C(=O)-O-, -N(R^n)-SO$_2$-, -C(=O)-, -C(=O)-O-, -het-, -C(=O)-N(R^n)-, -PO(OR^c)O- and -P(O)O-, where s is 0-2 and het is a mono- or bicyclic 5, 6, 7, 9 or 10 member heterocyclic ring, each ring containing 1-4 heteroatoms selected from N, O and S, where the heterocyclic ring may be saturated, partially saturated, or aromatic and any N or S being optionally oxidized, the heterocyclic ring being substituted with 0-3 R^h.

V is absent or is an optionally substituted bivalent group selected from C_1-C_6alkyl, C_3-C_8cycloalkyl, C_0-C_6alkyl-C_6-C_{10}aryl, and C_0-C_6alky-het, where the substituents on any alkyl are 1-3 R^a and the substituents on any aryl or het are 1-3 R^d.

W is selected from the group; hydrogen, -OR^o, -SR^m, -$NR^nR^{n'}$, -NH-C(=O)-O-R^c, -NH-C(=O)-$NR^nR^{n'}$, -NH-C(=O)-R^c, -NH-SO_2-R^s, -NH-SO_2-$NR^nR^{n'}$, -NH-SO_2-NH-C(=O)-R^c, -NH-C(=O)-NH-SO_2-R^s, -C(=O)-NH—C(=O)-O-R^c, -C(=O)-NH-C(=O)-R^c, -C(=O)-NH-C(=O)-$NR^nR^{n'}$, -C(=O)-NH-SO_2-R^s, -C(=O)-NH-SO_2-$NR^nR^{n'}$, -C(=S)-$NR^nR^{n'}$, -SO_2-R^s, -SO_2-O-R^s, -SO_2-$NR^nR^{n'}$, -SO_2-NH-C(=O)-O-R^c, -SO_2-NH-C(=O)-$NR^nR^{n'}$, -SO_2-NH-C(=O)-R^c, -O-C(=O)-$NR^nR^{n'}$, -O-C(=O)-R^c, -O-C(=O)-NH-C(=O)-R^c, -O-C(=O)-NH-SO_2-R^s and -O-SO_2-R^s.

R is selected from -C(=O)-R^z, -C(=O)-H, -CH_2(OH) and -CH_2O-C(=O)-C_1-C_6alkyl.

R^a is $R^{a'}$ or $R^{a''}$ substituted with 1-3 $R^{a'}$.

$R^{a'}$ is selected from the group; hydrogen, halo(F. Cl, Br, I), cyano, isocyanate, carboxy, carboxy-C_1-C_{11}alkyl, amino, amino-C_1-C_8alkyl, aminocarbonyl, carboxamido, carbamoyl, carbamoyloxy, formyl, formyloxy, azido, nitro, imidazoyl, ureido, thioureido, thiocyanato, hydroxy, C_1-C_6alkoxy, mercapto, sulfonamido, het, phenoxy, phenyl, benzamido, tosyl, morpholino, morpholinyl, piperazinyl, piperidinyl, pyrrolinyl. imidazolyl and indolyl.

$R^{a''}$ is selected from the group C_0-C_{10}alkyl-Q-C_0-C_6alkyl, C_0-C_{10}alkenyl-Q-C_0-C_6alkyl, C_0-C_{10}alkynyl-Q-C_0-C_6alkyl, C_3-C_{11}cycloalkyl-Q-C_0-C_6alkyl, C_3-C_{10}cycloalkenyl-Q-C_0-C_6alkyl, C_1-C_6alkyl-C_6-C_{12}aryl-Q-C_0-C_6alkyl, C_6-C_{10}aryl-C_1-C_6alkyl-Q-C_0-C_6alkyl, C_0-C_6alkyl-het-Q-C_0-C_6alkyl, C_0-C_6alkyl-Q-het-C_0-C_6alkyl, het-C_0-C_6alkyl-Q-C_0-C_6alkyl, C_0-C_6alkyl-Q-C_6-C_{12}aryl and Q-C_1-C_6alkyl.

R^c is selected from hydrogen and substituted or unsubstituted; C_1-C_{10}alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_3-C_{11}cycloalkyl, C_3-C_{10}cycloalkenyl, C_1-C_6alkyl-C_6-C_{12}aryl. C_6-C_{10}aryl-C_1-C_6alkyl, C_1-C_6alkyl-het, het-C_1-C_6alkyl, C_6-C_{12}aryl and het, where the substituents on any alkyl, alkenyl or alkynyl are 1-3 R^a and the substituents on any aryl or het are 1-3 R^d.

R^d is selected from R^p and R^h.

R^h is selected from the group OH, OCF_3, OR^c, SR^m, halo(F, Cl. Br, I), CN, isocyanate, NO_2, CF_3, C_0-C_6alkyl-$NR^nR^{n'}$, C_0-C_6alkyl-C(=O)-$NR^nR^{n'}$, C_0-C_6alkyl-C(=O)-R^a, C_1-C_8alkyl, C_1-C_8alkoxy, C_2-C_8alkenyl, C_2-C_8alkynyl, C_3-C_6cycloalkyl, C_3-C_6cycloalkenyl, C_1-C_6alkyl-phenyl, phenyl-C_1-C_6alkyl, C_1-C_6alkyloxycarbonyl, phenyl-C_0-C_6alkyloxy, C_1-C_6alkyl-het, het-C_1-C_6alkyl, SO_2-het, -O-C_6-C_{12}aryl, -SO_2-C_6-C_{12}aryl, -SO_2-C_1-C_6alkyl and het, where any alkyl, alkenyl or alkynyl may optionally be substituted with 1-3 groups selected from OH, halo(F, Cl, Br, I), nitro, amino and aminocarbonyl and the substituents on any aryl or het are 1-2 hydroxy, halo(F, Cl, Br, I), CF_3, C_1-C_6alkyl, C_1-C_6alkoxy, nitro and amino.

R^m is selected from S-C_1-C_6alkyl, C(=O)-C_1-C_6alkyl, C(=O)-$NR^nR^{n'}$, C_1-C_6alkyl, halo(F, Cl, Br, I)-C_1-C_6alkyl, benzyl and phenyl.

R^n is selected from the group R^c, NH-C(=O)-O-R^c, NH-C(=O)-R^c, NH-C(=O)-NHR^c, NH-SO_2-R^s, NH-SO_2-NH-C(=O)-R^c, NH-C(=O)-NH-SO_2-R^s, C(=O)-O-R^c, C(=O)-R^c, C(=O)-NHR^c, C(=O)-NH-C(=O)-O-R^c, C(=O)-NH-C(=O)-R^c, C(=O)-NH-SO_2-R^s, C(=O)-NH-SO_2-NHR^s, SO_2-R^s, SO_2-O-R^s, SO_2-N(R^c)$_2$, SO_2-NH-C(=O)-O-R^c, SO_2-NH-C(=O)-O-R^c and SO_2-NH-C(=O)-R^c.

$R^{n'}$ is selected from hydrogen, hydroxy and substituted or unsubstituted C_1-C_{11}alkyl, C_1-C_{11}alkoxy, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_3-C_{11}cycloalkyl, C_3-C_{10}cycloalkenyl, C_1-C_6alkyl-C_6-C_{12}aryl, C_6-C_{10}aryl-C_1-C_6alkyl, C_6-C_{10}aryl-C_0-C_6alkyloxy, C_1-C_6alkyl-het, het-C_1-C_6alkyl, C_6-C_{12}aryl, het, C_1-C_6alkylcarbonyl, C_1-C_8alkoxycarbonyl, C_3-C_8cycloalkylcarbonyl, C_3-C_8cycloalkoxycarbonyl, C_6-C_{11}aryloxycarbonyl, C_7-C_{11}arylalkoxycarbonyl, heteroarylalkoxycarbonyl, heteroarylalkylcarbonyl, heteroarylcarbonyl, heteroarylalkylsulfonyl, heteroarylsulfonyl, C_1-C_6alkylsulfonyl and C_6-C_{10}arylsulfonyl, where the substituents on any alkyl, alkenyl or alkynyl are 1-3 R^a and the substituents on any aryl, het or heteroaryl are 1-3 R^d.

Optionally, R^n and $R^{n'}$ taken together with the common nitrogen to which they are attached may from an optionally substituted heterocycle selected from morpholinyl, piperazinyl, thiamorpholinyl, pyrrolidinyl, imidazolidinyl, indolinyl, isoindolinyl, 1,2,3,4-tetrahydro-quinolinyl, 1,2,3,4-tetrahydro-isoquinolinyl, thiazolidinyl and azabicyclononyl, where the substituents are 1-3 R^a.

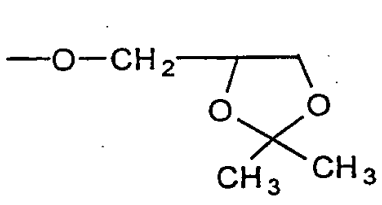
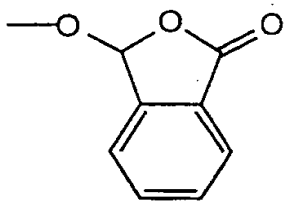
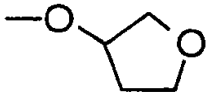
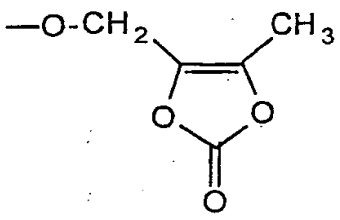
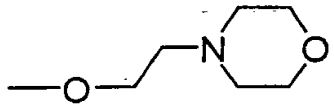
R^o is selected from hydrogen and substituted or unsubstituted C_1-C_6alkyl, C_1-C_6alkylcarbonyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_8cycloalkyl and benzoyl, where the substituents on any alkyl are 1-3 R^a and the substituents on any aryl are 1-3 R^p.

R^p is selected from the group; OH, halo(F, Cl. Br, I), CN, isocyanate, OR^c, SR^m, SOR^c, NO_2, CF_3, R^c, $NR^nR^{n'}$, N(R^n)-C(=O)-O-R^c, N(R^n)-C(=O)-R^c, C_0-C_6alkyl-SO_2-R^c, C_0-C_6alkyl-SO_2-$NR^nR^{n'}$, C(=O)-R^c, O-C(=O)-R^c, C(=O)-O-R^c and C(=O)-$NR^nR^{n'}$, where the substituents on any alkyl, alkenyl or alkynyl are 1-3 R^a and the substituents on any aryl or het are 1-3 R^d.

R^s is a substituted or unsubstituted group selected from; C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, C_3-C_8cycloalkyl, C_3-C_6cycloalkenyl, C_0-C_6alkyl-phenyl, phenyl-C_0-C_6alkyl, C_0-

C_6alkyl-het and het-C_0-C_6alkyl, where the substituents on any alkyl, alkenyl or alkynyl are 1-3 R^a and the substituents on any aryl or het are 1-3 R^d.

R^z is a substituted or unsubstituted group selected from; hydroxy, C_1-C_{11}alkoxy, C_3-C_{12}cycloalkoxy, C_8-C_{12}aralkoxy, C_8-C_{12}arcycloalkoxy, C_6-C_{10}aryloxy, C_3-C_{10}alkylcarbonyloxyalkyloxy, C_3-C_{10}alkoxycarbonyloxyalkyloxy, C_3-C_{10}alkoxycarbonylalkyloxy, C_5-C_{10}cycloalkylcarbonyloxyalkyloxy, C_5-C_{10}cycloalkoxycarbonyloxyalkyloxy, C_5-C_{10}cycloalkoxycarbonylalkyloxy, C_8-C_{12}aryloxycarbonylalkyloxy, C_8-C_{12}aryloxycarbonyloxyalkyloxy, C_8-C_{12}arylcarbonyloxyalkyloxy, C_5-C_{10}alkoxyalkylcarbonyloxyalkyloxy, $(R^n)(R^{n'})N(C_1$-C_{10}alkoxy)

and

where the substituents on any alkyl, alkenyl or alkynyl are 1-3 R^a and the substituentson any aryl or het are 1-3 R^d and pharmaceutically acceptable salts thereof.

Brief Description of the Drawings

FIGURE 1 A cartoon illustrating lymphocyte recruitment to a site of infection is provided. Lymphocyte rolling and adhesion to ICAM expressing cells (leukocytes, endothelium, epithelium) is shown.

FIGURE 2 A cartoon illustrating the human ICAM-1:LFA-1 receptor binding assay (protein/protein assay) is provided. Inhibition of the CD11a/CD18-ICAM-1 interaction is quantitated by adding known amounts of inhibitors to the protein/protein assay system described in Example 3.

FIGURE 3 A cartoon illustrating the human T Cell Adhesion Assay described in Example 4 is provided.

FIGURE 4 A cartoon illustrating the human T cell proliferation assay is provided. Cell proliferation is measured by tritiated thymidine uptake.

FIGURE 5 A cartoon illustrating the human one way mixed lymphocyte response is provided. Cell proliferation is measured by tritiated thymidine uptake.

Description of the Preferred Embodiments

A. Definitions

The term "LFA-1-mediated disorders" refers to pathological states caused by cell adherence interactions involving the LFA-1 receptor on lymphocytes. Examples of such disorders include T-cell inflammatory responses such as inflammatory skin diseases including psoriasis; responses associated with inflammatory bowel disease (such as Crohn's disease and ulcerative colitis); adult respiratory distress syndrome; dermatitis; meningitis; encephalitis; uveitic; allergic conditions such as eczema and asthma and other conditions involving infiltration of T-cells and chronic inflammatory responses; skin hypersensitivity reactions (including poison ivy and poison oak); atherosclerosis; leukocyte adhesion deficiency; autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus (SLE), diabetes mellitus, multiple sclerosis, Reynaud's syndrome, autoimmune thyroiditis, experimental autoimmune encephalomyelitis, Sjorgen's syndrome, type 1 diabetes, juvenile onset diabetes, and immune responses associated with delayed hypersensitivity mediated by cytokines and T-lymphocytes typically found in tuberculosis, sarcoidosis, polymyositis, granulomatosis and vasculitis; pernicious anemia; diseases involving leukocyte diapedesis; CNS inflammatory disorder, multiple organ injury syndrome secondary to septicaemia or trauma; autoimmune haemolytic anemia; myethemia gravis; antigen-antibody complex mediated diseases; all types of transplantations, including graft vs. host or host vs. graft disease; etc.

"Treating" such diseases includes therapy, prophylactic treatment, prevention of rejection of grafts, and induction of tolerance of grafts on a long-term basis.

The term "graft" as used herein refers to biological material derived from a donor for transplantation into a recipient. Grafts include such diverse material as, for example, isolated cells such as islet cells, tissue such as the amniotic membrane of a newborn, bone marrow, hematopoietic precursor cells, and organs such as skin, heart, liver, spleen, pancreas, thyroid lobe, lung, kidney, tubular organs (e.g., intestine, blood vessels, or esophagus), etc. The tubular organs can be used to replace damaged portions of esophagus, blood vessels, or bile duct. The skin grafts can be used not only for burns, but also as a dressing to damaged intestine or to close certain defects such as diaphragmatic hernia. The graft is derived from any mammalian source, including human, whether from cadavers or living donors. Preferably the graft is bone marrow or an organ such as heart and the donor of the graft and the host are matched for HLA class II antigens.

The term "mammal" refers to any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, horses, cats, cows, etc. Preferably, the mammal herein is human.

The term "mammalian host" as used herein refers to any compatible transplant recipient. By "compatible" is meant a mammalian host that will accept the donated graft. Preferably, the host is human. If both the donor of the graft and the host are human, they are preferably matched for HLA class II antigens so as to improve histocompatibility.

The term "donor" as used herein refers to the mammalian species, dead or alive, from which the graft is derived. Preferably, the donor is human. Human donors are preferably volunteer blood-related donors that are normal on physical examination and of the same major ABO blood group, because crossing major blood group barriers possibly prejudices survival of the allograft. It is, however, possible to transplant, for example, a kidney of a type O donor into an A, B or AB recipient.

The term "transplant" and variations thereof refers to the insertion of a graft into a host, whether the transplantation is syngeneic (where the donor and recipient are genetically identical), allogeneic (where the donor and recipient are of different genetic origins but of the same species), or xenogeneic (where the donor and recipient are from different species). Thus, in a typical scenario, the host is human and the graft is an isograft, derived from a human of the same or different genetic origins. In another scenario, the graft is derived from a species different from that into which it is transplanted, such as a baboon heart transplanted into a human recipient host, and including animals from phylogenically widely separated species, for example, a pig heart valve, or animal beta islet cells or neuronal cells transplanted into a human host.

The term "LFA-1 antagonist" as used herein generally refers to a benzoyl-amino acid (AA) derivative or a peptidomimetic thereof that acts as a competitive inhibitor of the CD11a and/or CD18 interaction with ICAM-1, soluble forms of ICAM-1 and bound or soluble forms of ICAM-2, ICAM-3 and telencephalin.

The term "immunosuppressive agent" as used herein for adjunct therapy refers to substances that act to suppress or mask the immune system of the host into which the graft is being transplanted. This would include substances that suppress cytokine production, down regulate or suppress self-antigen expression, or mask the MHC antigens. Examples of such agents include 2-amino-6-aryl-5-substituted pyrimidines (see U.S. Pat. No. 4,665,077, *supra*, the disclosure of which is incorporated herein by reference), azathioprine (or cyclophosphamide, if there is an adverse reaction to azathioprine); bromocryptine; glutaraldehyde (which masks the MHC antigens, as described in U.S. Pat. No. 4,120,649, *supra*); anti-idiotypic antibodies for MHC antigens and MHC fragments; cyclosporin A; steroids such as glucocorticosteroids, e.g., prednisone, methylprednisolone, and dexamethasone; cytokine or cytokine receptor antagonists including anti-interferon-ß, or -a antibodies; anti-tumor necrosis factor-a antibodies; anti-tumor necrosis factor-ß antibodies; anti-interleukin-2 antibodies and anti-IL-2 receptor antibodies; anti-L3T4 antibodies; heterologous anti-lymphocyte globulin; pan-T antibodies, preferably anti-CD3 or anti-CD4/CD4a antibodies; soluble peptide containing a LFA-3 binding domain (WO 90/08187 published 7/26/90), streptokinase; TGF-ß; streptodornase; RNA or DNA from the host; FK506; RS-61443;

deoxyspergualin; rapamycin; T-cell receptor (Cohen *et al.*, U.S. Pat. No. 5,114,721); T-cell receptor fragments (Offner *et al.*, *Science*, 251:430-432 (1991); copending U.S. Ser. No. 07/853,362 filed March 18, 1992, the disclosure of which is incorporated herein by reference; Howell, WO 90/11294; Ianeway, *Nature*, 341:482 (1989); and Vandenbark, WO 91/01133); and T-cell receptor antibodies (EP 340,109) such as T10B9. These agents are administered at the same time or at separate times from the CD11a or CD18 antagonists as used in this invention, and are used at the same or lesser dosages than as set forth in the art.

The preferred adjunct immunosuppressive agent will depend on many factors, including the type of disorder being treated including the type of transplantation being performed, as well as the patient's history, but a general overall preference is that the agent be selected from cyclosporin A, a glucocorticosteroid (most preferably prednisone or methylprednisolone), OKT-3 monoclonal antibody, azathioprine, bromocryptine, heterologous anti-lymphocyte globulin, or a mixture thereof.

"Increasing tolerance of a transplanted graft" by a host refers to prolonging the survival of a graft in a host in which it is transplanted, i.e., suppressing the immune system of the host so that it will better tolerate a foreign transplant.

The term "alkyl" means a branched or unbranched, saturated aliphatic hydrocarbon radical, having the number of carbon atoms specified, or if no number is specified, having up to 12 carbon atoms. Unless otherwise specified the term also encompasses unsaturated alkyls defined as "cycloalkyl", "alkenyl" and "alkynyl" below. Examples of preferred alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, 2-methylbutyl, 2,2-dimethylpropyl, n-hexyl, 2-methylpentyl, 2,2-dimethylbutyl, n-heptyl, 2-methylhexyl, and the like. The term "C_0-C_6 alkyl" and similar terms containing "C_0" means a covalent bond when the number of carbons is zero (C_0) or C_1-C_6 alkyl. If necessary to prevent a dangling valence the term "C_0" may include a hydrogen atom. A preferred "C_1-C_6 alkyl" group is methyl.

The term "substituted C_n-C_m alkyl" where m and n are integers identifying the range of carbon atoms contained in the alkyl group, denotes the above alkyl groups that are substituted by the groups listed or if no groups are listed one, two or three halogen, hydroxy, protected hydroxy, amino, protected amino, C_1-C_7 acyloxy, nitro, carboxy, protected carboxy, carbamoyl, carbamoyloxy, cyano, methylsulfonylamino or C_1-C_4 alkoxy groups. The substituted alkyl groups may be substituted once , twice or three times with the same or with different substituents.

Examples of the above substituted alkyl groups include but are not limited to; cyanomethyl, nitromethyl, hydroxymethyl, trityloxymethyl, propionyloxymethyl, aminomethyl, carboxymethyl, alkyloxycarbonylmethyl, allyloxycarbonylaminomethyl, carbamoyloxymethyl, methoxymethyl, ethoxymethyl, t-butoxymethyl, acetoxymethyl, chloromethyl, bromomethyl, iodomethyl, trifluromethyl, 6-hydroxyhexyl, 2,4-dichloro(n-butyl), 2-amino(iso-propyl), 2-carbamoyloxyethyl and the like. A preferred group of examples within the above "C_1-C_{12}

substituted alkyl" group includes the substituted methyl group, e.g. a methyl group substituted by the same substituents as the "substituted C_n-C_m alkyl" group. Examples of the substituted methyl group include groups such as hydroxymethyl, protected hydroxymethyl (e.g. tetrahydropyranyloxymethyl), acetoxymethyl, carbamoyloxymethyl, trifluoromethyl, chloromethyl, bromomethyl and iodomethyl.

The terms "C_1-C_{12} alkyloxy" or "C_1-C_{12} alkoxy" are used interchangeably herein and denote groups such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, t-butoxy and like groups.

The terms "C_1-C_{12} acyloxy" or "C_1-C_{12} alkanoyloxy" are used interchangeably and denote herein groups such as formyloxy, acetoxy, propionyloxy, butyryloxy, pentanoyloxy, hexanoyloxy, heptanoyloxy, and the like.

The terms "C_1-C_{12} alkylcarbonyl", "C_1-C_{12} alkanoyl" and "C_1-C_{12} acyl" are used interchangeably herein encompass groups such as formyl, acetyl, propionyl, butyryl, pentanoyl, hexanoyl, heptanoyl, benzoyl and the like.

The term "cycloalkyl" as used herein refers to a mono-, bi-, or tricyclic saturated or unsaturated ring, each ring having from 3 to 14 carbon atoms and preferably 3 to 7 carbon atoms. Optionally any ring carbon may be oxidized to from a carbonyl.

The term "alkenyl" means a branched or unbranched hydrocarbon radical having the number of carbon atoms designated containing one or more carbon-carbon double bonds, each double bond being independently cis, trans, or a nongeometric isomer.

The term "alkynyl" means a branched or unbranched hydrocarbon radical having the number of carbon atoms designated containing one or more carbon-carbon triple bonds.

The terms "C_1-C_{12} alkylthio" and "C_1-C_{12} substituted alkylthio" denote C_1-C_{12} alkyl and C_1-C_{12} substituted alkyl groups, respectively, attached to a sulfur which is in turn the point of attachment for the alkylthio or substituted alkylthio group to the group or substituent designated.

The term "aryl" when used alone means a homocyclic aromatic radical whether or not fused having the number of carbon atoms designated. Preferred aryl groups include phenyl, napthyl, biphenyl, phenanthrenyl, naphthacenyl, and the like (see e.g. *Lang's Handbook of Chemistry* (Dean, J. A., ed.) 13^{th} ed. Table 7-2 [1985]).

The term "substituted phenyl" or "substituted aryl" denotes a phenyl group or aryl group substituted with one, two or three substituents chosen from the groups listed or those selected from; halogen(F, Cl, Br, I), hydroxy, protected hydroxy, cyano, nitro, C_1-C_6alkyl, C_1-C_6alkoxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, aminomethyl, protected aminomethyl, trifluoromethyl N-(methylsulfonylamino) or other groups specified.

Examples of the term "substituted phenyl" includes but is not limited to a mono- or di(halo)phenyl group such as 4-chlorophenyl, 2,6-dichlorophenyl, 2,5-dichlorophenyl, 3,4-

dichlorophenyl, 3-chlorophenyl, 3-bromophenyl, 4-bromophenyl, 3,4-dibromophenyl, 3-chloro-4-fluorophenyl, 2-fluorophenyl and the like; a mono- or di(hydroxy)phenyl group such as 4-hydroxyphenyl, 3-hydroxyphenyl, 2,4-dihydroxyphenyl, the protected-hydroxy derivatives thereof and the like; a nitrophenyl group such as 3- or 4-nitrophenyl; a cyanophenyl group, for example, 4-cyanophenyl; a mono- or di(lower alkyl)phenyl group such as 4-methylphenyl, 2,4-dimethylphenyl, 2-methylphenyl, 4-(iso-propyl)phenyl, 4-ethylphenyl, 3-(n-propyl)phenyl and the like; a mono or di(alkoxy)phenyl group, for example, 2,6-dimethoxyphenyl, 4-methoxyphenyl, 3-ethoxyphenyl, 4-(isopropoxy)phenyl, 4-(t-butoxy)phenyl, 3-ethoxy-4-methoxyphenyl and the like; 3- or 4- trifluoromethylphenyl; a mono- or dicarboxyphenyl or (protected carboxy)phenyl group such 4-carboxyphenyl; a mono- or di(hydroxymethyl)phenyl or (protected hydroxymethyl)phenyl such as 3-(protected hydroxymethyl)phenyl or 3,4-di(hydroxymethyl)phenyl; a mono- or di(aminomethyl)phenyl or (protected aminomethyl)phenyl such as 2-(aminomethyl)phenyl or 2,4-(protected aminomethyl)phenyl; or a mono- or di(N-(methylsulfonylamino))phenyl such as 3-(N-methylsulfonylamino))phenyl. Also, the term "substituted phenyl" represents disubstituted phenyl groups wherein the substituents are different, for example, 3-methyl-4-hydroxyphenyl, 3-chloro-4-hydroxyphenyl, 2-methoxy-4-bromophenyl, 4-ethyl-2-hydroxyphenyl, 3-hydroxy-4-nitrophenyl, 2-hydroxy-4-chlorophenyl and the like. Preferred substituted phenyl groups include the 2- and 3-trifluoromethylphenyl, the 4-hydroxyphenyl, the 2-aminomethylphenyl and the 3-(N-(methylsulfonylamino))phenyl groups.

The term "arylalkyl" means one, two, or three aryl groups having the number of carbon atoms designated, appended to an alkyl radical having the number of carbon atoms designated including but not limited to; benzyl, napthylmethyl, phenethyl, benzhydryl (diphenylmethyl), trityl, and the like. A preferred arylalkyl group is the benzyl group.

The term "substituted C_6-C_{10}aryl-C_1-C_8alkyl" denotes a C_1-C_8alkyl group substituted at any carbon with a C_6-C_{10}aryl group bonded to the alkyl group through any aryl ring position and substituted on the C_1-C_8alkyl portion with one, two or three groups chosen from halogen (F, Cl, Br, I), hydroxy, protected hydroxy, amino, protected amino, C_1-C_7acyloxy, nitro, carboxy, protected carboxy, carbamoyl, carbamoyloxy, cyano, C_1-C_6alkylthio, N-(methylsulfonylamino) or C_1-C_4alkoxy. Optionally the aryl group may be substituted with one, two, or three groups chosen from halogen, hydroxy, protected hydroxy, nitro, C_1-C_6alkyl, C_1-C_4alkoxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, aminomethyl, protected aminomethyl, or an N-(methylsulfonylamino) group. As before, when either the C_1-C_8alkyl portion or the aryl portion or both are disubstituted, the substituents can be the same or different.

Examples of the term "substituted C_6-C_{10}aryl-C_1-C_8alkyl" include groups such as 2-phenyl-1-chloroethyl, 2-(4-methoxyphenyl)ethyl, 2,6-dihydroxy-4-phenyl(n-hexyl), 5-cyano-3-methoxy-2-phenyl(n-pentyl), 3-(2,6-dimethylphenyl)n-propyl, 4-chloro-3-aminobenzyl, 6-(4-

methoxyphenyl)-3-carboxy(n-hexyl), 5-(4-aminomethyl phenyl)-3-(aminomethyl)(n-pentyl), and the like.

The term "carboxy-protecting group" as used herein refers to one of the ester derivatives of the carboxylic acid group commonly employed to block or protect the carboxylic acid group while reactions are carried out on other functional groups on the compound. Examples of such carboxylic acid protecting groups include 4-nitrobenzyl, 4-methoxybenzyl, 3,4-dimethoxybenzyl, 2,4-dimethoxybenzyl, 2,4,6-trimethoxybenzyl, 2,4,6-trimethylbenzyl, pentamethylbenzyl, 3,4-methylenedioxybenzyl, benzhydryl, 4,4'-dimethoxybenzhydryl, 2,2',4,4'-tetramethoxybenzhydryl, t-butyl, t-amyl, trityl,4-methoxytrityl, 4,4'-dimethoxytrityl, 4,4',4"-trimethoxytrityl, 2-phenylprop-2-yl, trimethylsilyl, t-butyldimethylsilyl, phenacyl, 2,2,2-trichloroethyl, b-(trimethylsilyl)ethyl, b-(di(n-butyl)methylsilyl)ethyl, p-toluenesulfonylethyl, 4-nitrobenzylsulfonylethyl, allyl, cinnamyl, 1-(trimethylsilylmethyl)prop-1-en-3-yl, and like moieties. The species of carboxy-protecting group employed is not critical so long as the derivatized carboxylic acid is stable to the condition of subsequent reaction(s) on other positions of the benzodiazepinedione molecule and can be removed at the appropriate point without disrupting the remainder of the molecule. In particular, it is important not to subject the carboxy-protected benzodiazepinedione molecule to strong nucleophilic bases or reductive conditions employing highly activated metal catalysts such as Raney nickel. (Such harsh removal conditions are also to be avoided when removing amino-protecting groups and hydroxy-protecting groups, discussed below.) Preferred carboxylic acid protecting groups are the allyl and p-nitrobenzyl groups. Similar carboxy-protecting groups used in the cephalosporin, penicillin and peptide arts can also be used to protect a carboxy group substituents of the benzodiazepinedione. Further examples of these groups are found in E. Haslam, "Protective Groups in Organic Chemistry", J. G. W. McOmie, Ed., Plenum Press, New York, N.Y., 1973, Chapter 5, and T.W. Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons, New York, NY, 1981, Chapter 5. The term "protected carboxy" refers to a carboxy group substituted with one of the above carboxy-protecting groups.

As used herein the term "amide-protecting group" refers to any group typically used in the peptide art for protecting the peptide nitrogens from undesirable side reactions. Such groups include p-methoxyphenyl, 3,4-dimethoxybenzyl, benzyl, O-nitrobenzyl, di-(p-methoxyphenyl)methyl, triphenylmethyl, (p-methoxyphenyl)diphenylmethyl, diphenyl-4-pyridylmethyl, m-2-(picolyl)-N'-oxide, 5-dibenzosuberyl, trimethylsilyl, t-butyl dimethylsilyl, and the like. Further descriptions of these protecting groups can be found in "Protective Groups in Organic Synthesis", by Theodora W. Greene, 1981, John Wiley and Sons, New York.

Unless otherwise specified, the terms "heterocyclic group" or "heterocyclic" or "HET", "het" or "heterocyclyl" are used interchangeably as used herein refer to any mono-, bi-, or tricyclic saturated, unsaturated, or aromatic ring having the number of atoms designated where at least one ring is a 5-, 6- or 7-membered ring containing from one to four heteroatoms selected from the group nitrogen, oxygen, and sulfur (*Lang's Handbook of Chemistry, supra*). Typically, the 5-

membered ring has 0 to 2 double bonds and the 6- or 7-membered ring has 0 to 3 double bonds and the nitrogen, carbon or sulfur atoms in the ring may optionally be oxidized (e.g. NO_2, C=O and SO_2) and any nitrogen heteroatom may optionally be quaternized. Included in the definition are any bicyclic groups where any of the above heterocyclic rings are fused to a benzene ring. Heterocyclics in which oxygen and sulfur are the heteroatom are preferred when the heterocycly forms all or a part of "D" in Formula I.

The following ring systems are examples of the heterocyclic (whether substituted or unsubstituted) radicals denoted by the term "heterocylic" or het: thienyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, thiadiazolyl, oxadiazolyl, tetrazolyl, thiatriazolyl, oxatriazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, thiazinyl, oxazinyl, triazinyl, thiadiazinyl, oxadiazinyl, dithiazinyl, dioxazinyl, oxathiazinyl, tetrazinyl, thiatriazinyl, oxatriazinyl, dithiadiazinyl, imidazolinyl, dihydropyrimidyl, tetrahydropyrimidyl, tetrazolo[1,5-b]pyridazinyl and purinyl, as well as benzo-fused derivatives, for example benzoxazolyl, benzofuryl, benzothiazolyl, benzothiadiazolyl, benzotriazolyl, benzoimidazolyl and indolyl.

Heterocyclic 5-membered ring systems containing a sulfur or oxygen atom and one to three nitrogen atoms are also suitable for use in the instant invention. Examples of such preferred groups include thiazolyl, in particular thiazol-2-yl and thiazol-2-yl N-oxide, thiadiazolyl, in particular 1,3,4-thiadiazol-5-yl and 1,2,4-thiadiazol-5-yl, oxazolyl, preferably oxazol-2-yl, and oxadiazolyl, such as 1,3,4-oxadiazol-5-yl, and 1,2,4-oxadiazol-5-yl. A group of further preferred examples of 5-membered ring systems with 2 to 4 nitrogen atoms include imidazolyl, preferably imidazol-2-yl; triazolyl, preferably 1,3,4-triazol-5-yl; 1,2,3-triazol-5-yl, 1,2,4-triazol-5-yl, and tetrazolyl, preferably 1H-tetrazol-5-yl. A preferred group of examples of benzo-fused derivatives are benzoxazol-2-yl, benzthiazol-2-yl and benzimidazol-2-yl.

Further suitable specific examples of the above heterocylic ring systems are 6-membered ring systems containing one to three nitrogen atoms. Such examples include pyridyl, such as pyrid-2-yl, pyrid-3-yl, and pyrid-4-yl; pyrimidyl, preferably pyrimid-2-yl and pyrimid-4-yl; triazinyl, preferably 1,3,4-triazin-2-yl and 1,3,5-triazin-4-yl; pyridazinyl, in particular pyridazin-3-yl, and pyrazinyl. The pyridine N-oxides and pyridazine N-oxides and the pyridyl, pyrimid-2-yl, pyrimid-4-yl, pyridazinyl and the 1,3,4-triazin-2-yl radicals, are a preferred group.

The substituents for the optionally substituted heterocyclic ring systems, and further examples of the 5- and 6-membered ring systems discussed above can be found in W. Druckheimer *et al.*, U.S. Patent No. 4,278,793.

Another preferred group of "heterocyclics" or "het" include; 1,3-thiazol-2-yl, 4-(carboxymethyl)-5-methyl-1,3-thiazol-2-yl, 4-(carboxymethyl)-5-methyl-1,3-thiazol-2-yl sodium salt, 1,2,4-thiadiazol-5-yl, 3-methyl-1,2,4-thiadiazol-5-yl, 1,3,4-triazol-5-yl, 2-methyl-1,3,4-triazol-5-yl, 2-hydroxy-1,3,4-triazol-5-yl, 2-carboxy-4-methyl-1,3,4-triazol-5-yl sodium salt, 2-carboxy-4-

methyl-1,3,4-triazol-5-yl, 1,3-oxazol-2-yl, 1,3,4-oxadiazol-5-yl, 2-methyl-1,3,4-oxadiazol-5-yl, 2-(hydroxymethyl)-1,3,4-oxadiazol-5-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-thiadiazol-5-yl, 2-thiol-1,3,4-thiadiazol-5-yl, 2-(methylthio)-1,3,4-thiadiazol-5-yl, 2-amino-1,3,4-thiadiazol-5-yl, 1H-tetrazol-5-yl, 1-methyl-1H-tetrazol-5-yl, 1-(1-(dimethylamino)eth-2-yl)-1H-tetrazol-5-yl, 1-(carboxymethyl)-1H-tetrazol-5-yl, 1-(carboxymethyl)-1H-tetrazol-5-yl sodium salt, 1-(methylsulfonic acid)-1H-tetrazol-5-yl, 1-(methylsulfonic acid)-1H-tetrazol-5-yl sodium salt, 2-methyl-1H-tetrazol-5-yl, 1,2,3-triazol-5-yl, 1-methyl-1,2,3-triazol-5-yl, 2-methyl-1,2,3-triazol-5-yl, 4-methyl-1,2,3-triazol-5-yl, pyrid-2-yl N-oxide, 6-methoxy-2-(n-oxide)-pyridaz-3-yl, 6-hydroxypyridaz-3-yl, 1-methylpyrid-2-yl, 1-methylpyrid-4-yl, 2-hydroxypyrimid-4-yl, 1,4,5,6-tetrahydro-5,6-dioxo-4-methyl-as-triazin-3-yl, 1,4,5,6-tetrahydro-4-(formylmethyl)-5,6-dioxo-as-triazin-3-yl, 2,5-dihydro-5-oxo-6-hydroxy-astriazin-3-yl, 2,5-dihydro-5-oxo-6-hydroxy-as-triazin-3-yl sodium salt, 2,5-dihydro-5-oxo-6-hydroxy-2-methyl-astriazin-3-yl sodium salt, 2,5-dihydro-5-oxo-6-hydroxy-2-methyl-as-triazin-3-yl, 2,5-dihydro-5-oxo-6-methoxy-2-methyl-as-triazin-3-yl, 2,5-dihydro-5-oxo-as-triazin-3-yl, 2,5-dihydro-5-oxo-2-methyl-as-triazin-3-yl, 2,5-dihydro-5-oxo-2,6-dimethyl-as-triazin-3-yl, tetrazolo[1,5-b]pyridazin-6-yl and 8-aminotetrazolo[1,5-b]-pyridazin-6-yl.

An alternative group of "heterocyclics" includes; 4-(carboxymethyl)-5-methyl-1,3-thiazol-2-yl, 4-(carboxymethyl)-5-methyl-1,3-thiazol-2-yl sodium salt, 1,3,4-triazol-5-yl, 2-methyl-1,3,4-triazol-5-yl, 1H-tetrazol-5-yl, 1-methyl-1H-tetrazol-5-yl, 1-(1-(dimethylamino)eth-2-yl)-1H-tetrazol-5-yl, 1-(carboxymethyl)-1H-tetrazol-5-yl, 1-(carboxymethyl)-1H-tetrazol-5-yl sodium salt, 1-(methylsulfonic acid)-1H-tetrazol-5-yl, 1-(methylsulfonic acid)-1H-tetrazol-5-yl sodium salt, 1,2,3-triazol-5-yl, 1,4,5,6-tetrahydro-5,6-dioxo-4-methyl-as-triazin-3-yl, 1,4,5,6-tetrahydro-4-(2-formylmethyl)-5,6-dioxo-as-triazin-3-yl, 2,5-dihydro-5-oxo-6-hydroxy-2-methyl-as-triazin-3-yl sodium salt, 2,5-dihydro-5-oxo-6-hydroxy-2-methyl-as-triazin-3-yl, tetrazolo[1,5-b]pyridazin-6-yl, and 8-aminotetrazolo[1,5-b]pyridazin-6-yl.

Bivalent radicals L, whether branched or unbranched, derived from alkanes, alkenes, alkadienes, alkynes, alkadiynes, and arenes optionally containing O, N and/or S atoms, or homo- and heterocycles either aromatic or aliphatic, are designated by adding a free valence "-" to both ends of the corresponding monovalent radical. Atoms bearing the free valences may include any C, O, N or S.

"Pharmaceutically acceptable salts" include both acid and base addition salts. "Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases and which are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, carbonic acid, phosphoric acid and the like, and organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic, and sulfonic classes of organic acids such as formic acid, acetic acid, propionic acid, glycolic acid, gluconic acid, lactic acid, pyruvic acid, oxalic acid, malic acid, maleic acid, maloneic acid, succinic acid, fumaric acid, tartaric acid, citric acid, aspartic acid, ascorbic acid, glutamic acid, anthranilic acid, benzoic acid,

cinnamic acid, mandelic acid, embonic acid, phenylacetic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicyclic acid and the like.

"Pharmaceutically acceptable base addition salts" include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Particularly preferred are the ammonium, potassium, sodium, calcium and magnesium salts. Salts derived from pharmaceutically acceptable organic nontoxic bases includes salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-diethylaminoethanol, trimethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperizine, piperidine, N-ethylpiperidine, polyamine resins and the like. Particularly preferred organic non-toxic bases are isopropylamine, diethylamine, ethanolamine, trimethamine, dicyclohexylamine, choline, and caffeine.

The term "prodrug" as used herein means a derivative or precursor of a parent drug molecule that enhances pharmaceutically desirable characteristics or properties (e.g. transport, bioavailablity, pharmacodynamics, etc.) and that requires biotransformation, either spontaneous or enzymatic, within the organism to release the active parent drug. Examples of carboxylic prodrugs include precursors such as aldehydes, alcohol's or amines or derivatives such as esters

B. Uses

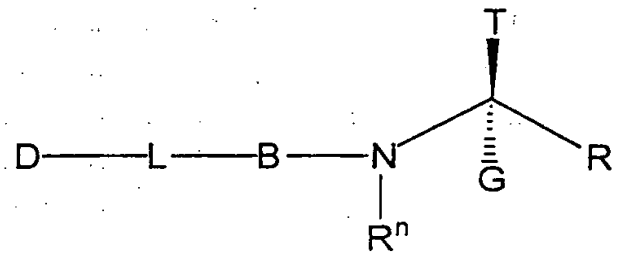
The LFA-1 and/or Mac-1 antagonists of this invention are useful for therapeutic use in those diseases and conditions for which inhibition or modulation of the LFA-1 and/or Mac-1 interaction with ICAM, especially ICAM-1, is indicated. Such diseases and conditions include: T-cell inflammatory responses such as inflammatory skin diseases including psoriasis; responses associated with inflammatory bowel disease (such as Crohn's disease and ulcerative colitis); adult respiratory distress syndrome; dermatitis; meningitis; encephalitis; uveitis; allergic conditions such as eczema and asthma, psoriasis and other conditions involving infiltration of T-cells and chronic inflammatory responses; skin hypersensitivity reactions (including poison ivy and poison oak), allergic contact dermatitis; atherosclerosis; autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus (SLE), diabetes mellitus, multiple sclerosis, Reynaud's syndrome, autoimmune thyroiditis, experimental autoimmune encephalomyelitis, Sjorgen's syndrome, juvenile onset diabetes, and immune responses associated with delayed hypersensitivity mediated by cytokines and T-lymphocytes typically found in tuberculosis, sarcoidosis, polymyositis, granulomatosis and vasculitis; pernicious anemia; diseases involving leukocyte diapedesis; CNS inflammatory disorder, multiple organ injury syndrome secondary to septicaemia or trauma; autoimmune haemolytic anemia; myasthenia gravis; antigen-antibody complex mediated diseases; all types of transplantations, including graft vs. host or host vs. graft disease, HIV infection and the like.

Other leukocyte mediated diseases for which the instant competitive inhibitors may be used include: hemorrhagic shock, ischemia/reperfusion injury, bypass surgery, burns, stroke, post CABG surgery, vasculitis, cerebral edema (broader, restenosis, AMI and non Q wave MI.

C. Preferred Embodiments

1. CD11a/CD18:ICAM-1 Competitive Inhibitors

One embodiment of the invention comprises a compound represented by Formula I capable of inhibiting binding of the leukocyte LFA-1 receptor to its native *in vivo* ligand(s), especially ICAM-1. Preferred inhibitors include compounds represented by structural Formula I:



(I)

Referring to Formula I the following important structural features of the instant peptidiomimetic LFA-1 inhibitors can be identified:

a. The negatively charged acidic moiety R or prodrug form thereof;

b. The substituent T, a naturally occurring amino acid side chain and derivatives thereof;

c. The amide nitrogen(N) and substituents (R^n):

d. The substituted "benzoyl" ring B;

e. substituents of the B ring, namely R^p;

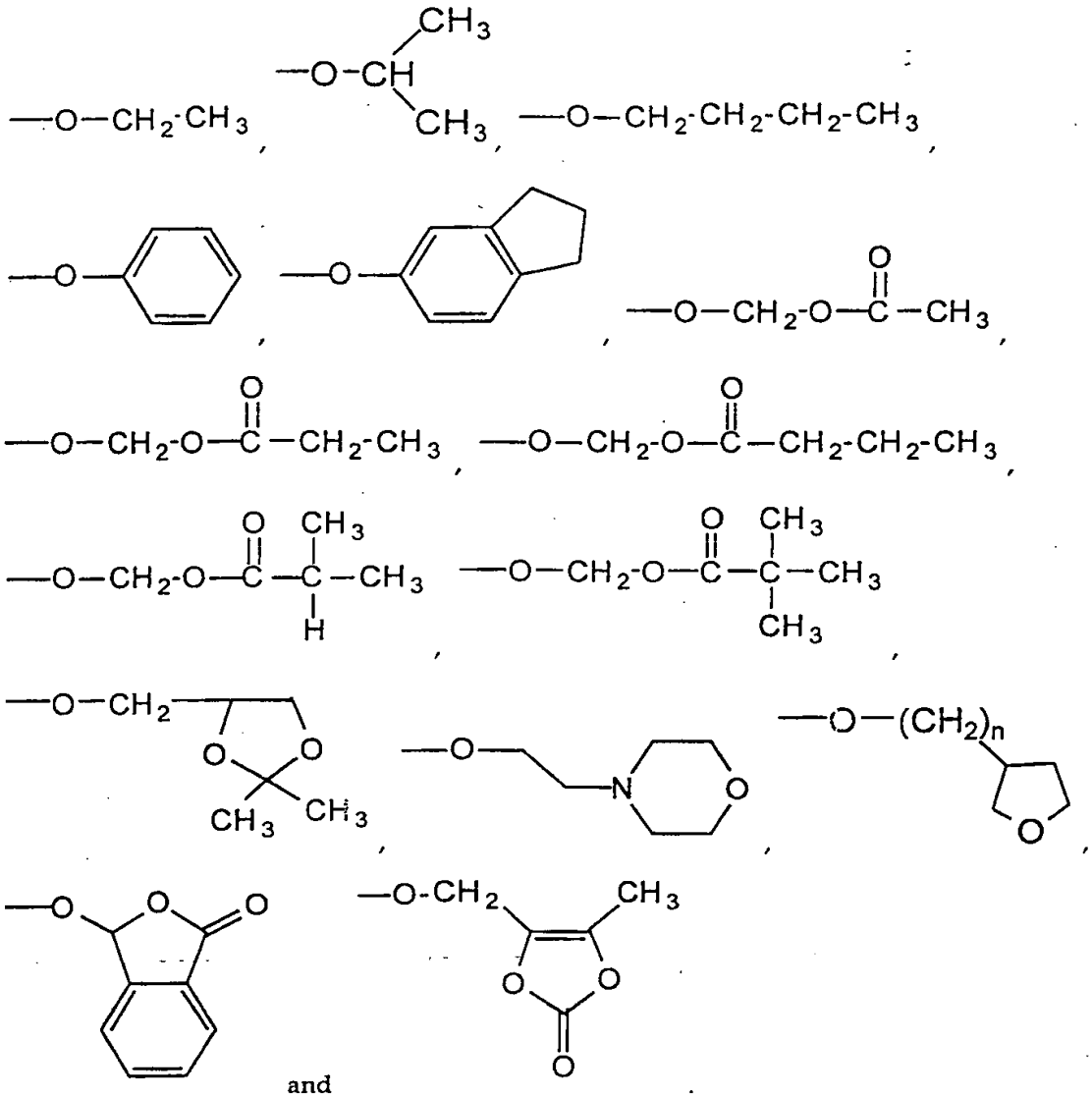
f. The spacer or linking moiety L.

g. The distal aromatic moiety D; and

h. substituents of D, namely R^d.

(a) The negatively charged acidic moiety R

The preferred negatively charged acidic moiety R is the carboxyl group (-COOH) or a prodrug thereof. Generally the carboxyl group R and prodrug forms thereof is designated $\overline{COR^z}$. Suitable R^z's include C_1-C_8alkoxy, C_1-C_8dialkyl-aminocarbonylmethoxy and C_6-C_{10}arylC_1-C_8dialkylaminocarbonylmethoxy. Other suitable prodrugs R^z includes the following groups:



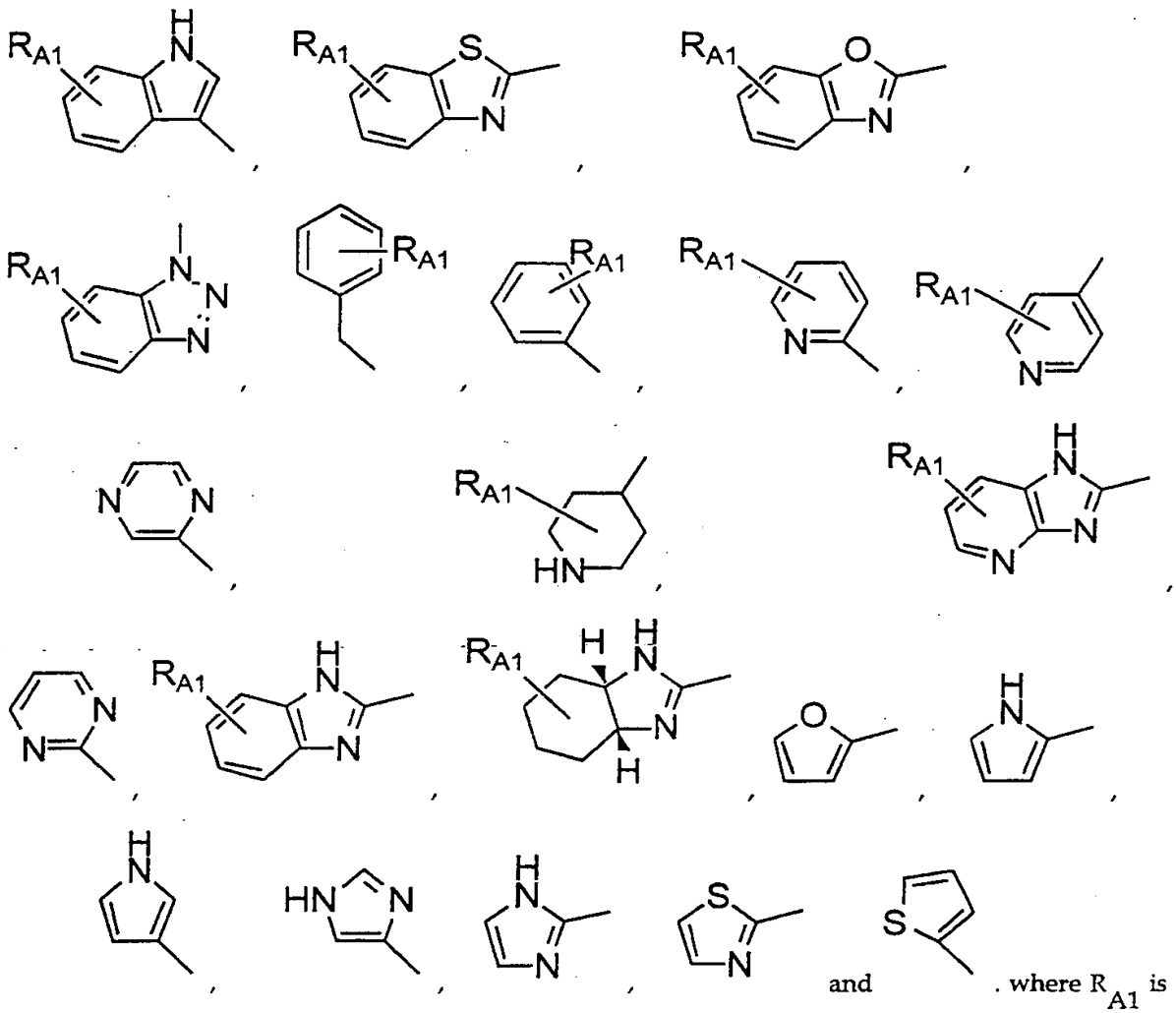
and

(b) The substituent T or U-Q-V-W

T of formula I is usually the sidechain of any α-amino acid, preferably the L configuration, or a homolog or derivative thereof. Preferably T will contain a hydrogen bond donating group such as $CONH_2$, NHCOH, NH_2, OH or NH. T will frequently be a 1-4 carbon alkane containing an amide, carbamate, ureido, sulfonamide and an optionally substituted phenyl or heterocycle. The heterocycle will usually be a 5 or 6 member ring with 1 or 2 hetero atoms selected from N, O and S. Such heterocycles include furan, thiophene, pyrrole, pyridine and piperidine. substituents include halogens such as chloro and fluro, nitro, cyano, alkyl and halo substituted alkyl, substituted or unsubstituted amides, amines, carbamates sulfonamides, ureidos and the like.

Examples of T will also include a lower alkyl, cycloalkyl, alkenyl or alkynyl substituted with an aromatic ring, especially a heteroaryl or C_6-C_{14}aryl, substituted with 0-3 R^d. Suitable aromatic rings include any mono-, bi-, or tricyclic saturated, unsaturated, or aromatic ring having

three to seven atoms in the ring, where at least one ring is a 5-, 6- or 7-membered ring containing from zero to four heteroatoms selected from the group nitrogen, oxygen, and sulfur, optionally substituted with R^d. Optionally the aromatic rings may be linked through a C_1-C_4 alkyl. Preferred ring's are substituted phenyl and het as defined above optionally substituted with R^d. More preferred optionally substituted aromatic ring 's are selected from the group;



and . where R_{A1} is 0-3 R^d or U-V-W.

Other optionally prefered substituents T are U-Q-V-W defined below. Specifically, T may preferably be -C_1-C_6alkyl-Q-V-W, where Q is -$N(R^n)$-, -C(=O)-, -$N(R^n)$C(=O)-, -C(=O)-$N(R^n)$-, -$N(R^n)$C(=O)-$N(R^n)$-, -$N(R^n)$C(=O)-O-, -O-C(=O)-$N(R^n)$-, -$N(R^n)S(=O)_2$-, -$S(=O)_2$-$N(R^n)$-, -C(=O)-O- or -O-; V may be het or absent and W is provided in Table 1.

Generally, each of U, Q, V and W are independently selected according to the Table 1 below. U, Q and V may also each independently be absent (i.e. one or more of U, Q, V may be a covalent bond).

Table 1

U	Q	V	W
$-C_1-C_6$alkyl-	-O-	$-C_1-C_6$alkyl-	R^a
$-C_2-C_6$alkenyl-	$-S(O)_{0-2}-$	$-C_3-C_8$cycloalkyl-	OR^o
$-C_1-C_6$alkynyl-	$-SO_2N(R^n)-$	$-C_0-C_6$alkyl-het-	SR^m
$-C_3-C_8$cycloalkyl-	$-N(R^n)-$	$-C_0-C_6$alkyl-C_6-C_{10}aryl-	$NR^nR^{n'}$
$-C_6-C_{10}$aryl-	$-N(R^n)C(=O)-$	$-C_2-C_6$alkenyl-	$NHCOOR^c$
	$-N(R^n)C(=O)-O-$	furan	$NHCONR^nR^{n'}$
	$-N(R^n)-SO_2-$	thiophene	$NHCOR^c$
	-C(=O)-	pyrrole	$NHSO_2R^s$
	-C(=O)-O-	phenyl	$NHSO_2NR^nR^{n'}$
	-het-	piperidine	$NHSO_2NHCOR^c$
	$-C(=O)-N(R^n)-$	piperazine	$NHCONHSO_2R^s$
	$-O-C(=O)-N(R^n)-$	morpholine	$CONHCOOR^c$
	$-PO(OR^c)-O-$	pyridine	$CONHCOR^c$
	-P(O)-O-		$CONHCONR^nR^{n'}$
			$CONHSO_2R^s$
			$CONHSO_2NR^nR^{n'}$
			$CSNR^nR^{n'}$
			SO_2-R^s

U	Q	V	W
			SO_3R^s
			$SO_2NR^nR^{n'}$
			OSO_2R^s
			$SO_2NHCOOR^c$

Where any alkyl, alkenyl or alkynyl is substituted with 0-3 R^a and any aryl or het are substituted with 0-3 R^d, and where R^a, R^c, R^d, R^m, R^n, $R^{n'}$, R^o and R^s are defined above.

More specifically, each of U, Q, V and W may be independently selected according to **Table 2** below.

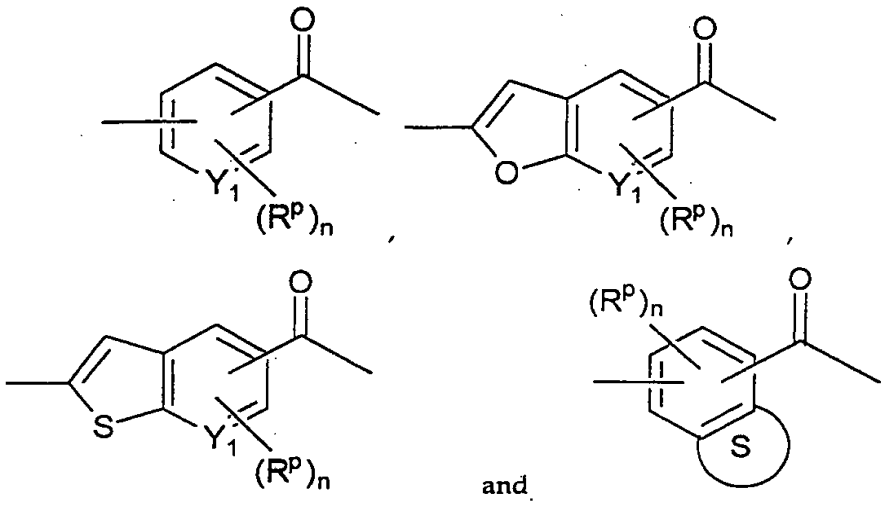
Table 2

U	Q	V	W
$-CH_2-$	$-N(R^n)C(=O)-$	2-thienyl	-
$-CH_2-$	$-N(R^n)C(=O)-$	2-furyl	-
$-CH_2-$	$-N(R^n)C(=O)-O-$	$-CH_2-CH=CH_2$	-
$-CH_2-$	$-C(=O)-NH_2$	-	-
$-CH_2-$	$-N(R^n)C(=O)-$	2-thienyl	halo
$-CH_2-$	-NH-C(=O)-NH-	phenyl	-CN
$-CH_2-CH_2-CH_2-$	$-N(R^n)-SO_2-$	2-thienyl	-
$-CH_2-$	-O-C(=O)-NH-	phenyl	methyl
$-CH_2-CH_2-CH_2-$	$-N(R^n)-SO_2-$	thioimidazole	$-NH-C(=O)-CH_3$
$-CH_2-CH_2-CH_2-$	$-NH-SO_2-$	phenyl	$-NH-C(=O)-CH_3$
$-CH_2-CH_2-CH_2-$	$-NH-SO_2-$	2-thienyl	-
$-CH_2-$	-NH-C(=O)-	pyrrole	tri-methyl
$-CH_2-CH_2-$	-NH-C(=O)-	3-chloro-2-thienyl	methylsulfonyl
$-CH_2-CH_2-$	-NH-C(=O)-	cyclopropyl	-
$-CH_2-CH_2-$	-NH-C(=O)-	2-thienyl	chloro

U	Q	V	W
$-CH_2-$	-NH-C(=O)-	2-furyl	methyl

(c) the substituents (R^n) for amide nitrogen N are lower alkyl or hydrogen and preferably hydrogen.

(d) The substituted "benzoyl" ring B is preferably selected from the group:



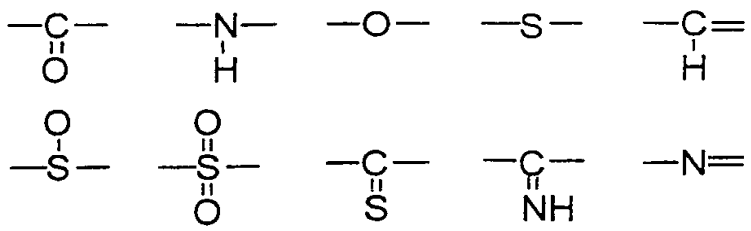
and

is a fused hetero- or homocyclic ring containing 5, 6 or 7 atoms, the ring being unsaturated, partially saturated or aromatic, the heteroatoms selected from 1-3 O, S or N, Y_1 is selected from CH or N, n is 0-3. Preferably B is a para-substituted benzoyl group.

(e) substituents of B (R^p) are defined above. Preferably when B is a para-substituted benzoyl group the remaining positions on B are substituted with one or more halo (F, Cl, Br) or lower alkyl groups.

(f) The linking group L

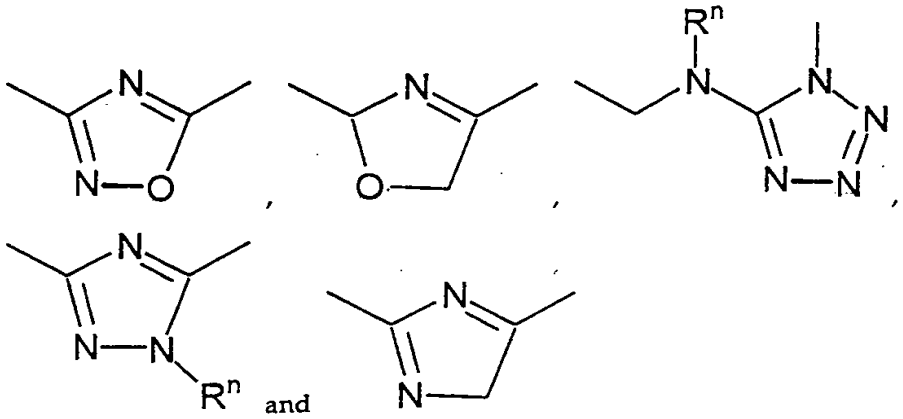
The length of the bivalent radical L appears to be important to optimal biological activity. By length is meant the distance between the "B" or benzoyl moiety (eg from the para position on B), including the amide or amide isostere bonded to the benzoyl moiety, and the distal group D. Preferably L is 3, 4 or 5 methylene ($-CH_2-$) equivalents in length depending on the atoms in L and the nature of D. Thus L is composed of L^1-L^3 and optionally L^4 and L^5. Each L^{1-5} is independently selected from oxo (-O-), $S(O)_s$, C(=O), $CR^{1-5}R^{1'-5'}$, CR^{1-5}, het, NR^n or N, where s is 0-2. For example, functional groups in L (in addition to $-CH_2-$ or $CR^{1-5}R^{1'-5'}$) include one or more of the following:



which may be located within the linker L (e.g. forming amides, imides, amidines, guanidinos, ureidos, carbamates, ethers, thioethers, ketones, sulfoxides, sulfonamides and the like) or combined in any combination, provided only that the compounds so produced are stable in aqueous solution and do not exceed the above stated length requirements. For example, preferred functional groups in L, other than a C_3-C_5 alkyl, are: ethers, diethers, ketones, alcohols, esters, amides, ureidos, carbamates, carbonates, sulfonamides, sulfoxides, sulfones, and combinations thereof. Preferred lengths for L are from 0 to 4 while most preferred lengths are 1 or 3 methylene equivalents. In counting atoms comprising L, only those atoms sequentially linking the benzoyl moiety B and the distyl group D are counted except when a homo- or heterocycle (eg het) comprises L in which case the fewest number of atoms separating these moieties are counted.

Preferred exemplary L bivalent linking groups include: -C_3-C_5-alkyl-, -C_3-C_5-alkenyl-, -$CH_2C(=O)NH$-, -CH_2NH-$C(=O)$-, -O-CH_2-$C(=O)$-, -CH_2-CH_2-$C(=O)$-, -$CH=CH$-$C(=O)NH$-CH_2-, -$CH=CH$-$C(=O)NH$-CH-(CH_3)-, -$CH(OH)$-CH_2-O-, -$CH(OH)$-CH_2-CH_2-, -CH_2-CH_2-$CH(OH)$-, -O-CH_2-$CH(OH)$-, -O-CH_2-$CH(OH)$-CH_2-, -O-CH_2-CH_2-$CH(OH)$-, -O-CH_2-CH_2-O-, -CH_2-CH_2-CH_2-O-, -CH_2-$CH(OH)$-CH_2-O-, -CH_2-CH_2-O-, -$CH(OH)$-CH_2-O-, -CH-(CH_3)-NH-$C(=O)$-, -CH_2-NH-SO_2-, -NH-SO_2-CH_2-, -CH_2-SO_2NH-, -SO_2NH-CH_2-, -$C(=O)$-NH-$C(=O)$-, -NH-$C(=O)$-NH-,-NH-$C(=O)$-NH-CH_2-, -CH_2-NH-$C(=O)$-NH-, -$C(=O)$-NH-CH_2-$C(=O)$-NH -, -NH-$C(=O)$-O- and -O-$C(=O)$-NH-.

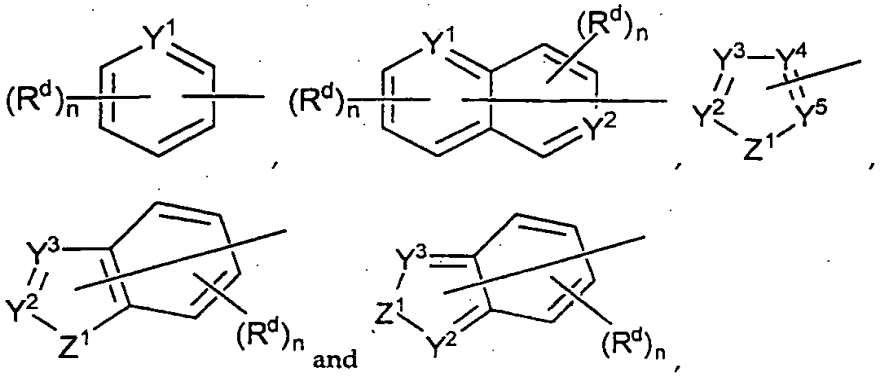
Preferred exemplary L bivalent linking groups containing a heterocycle include:



Any carbon in the bivalent linking groups may optionally be substituted with a halogen, especially fluorine.

(g) The distal moiety D may be a mono-, bi-, or tricyclic saturated, unsaturated, or aromatic ring, each ring having 5-, 6- or 7 atoms in the ring where the atoms in the ring are carbon or from 1-4 heteroatoms selected from; nitrogen, oxygen, and sulfur, each ring substituted with 0-3 R^d.

Optionally, D is an aromatic homocycle or aromatic heterocycle containing 1-3 heteroatoms selected from the group N, S and O, the homo- or hetero-cycles selected from:

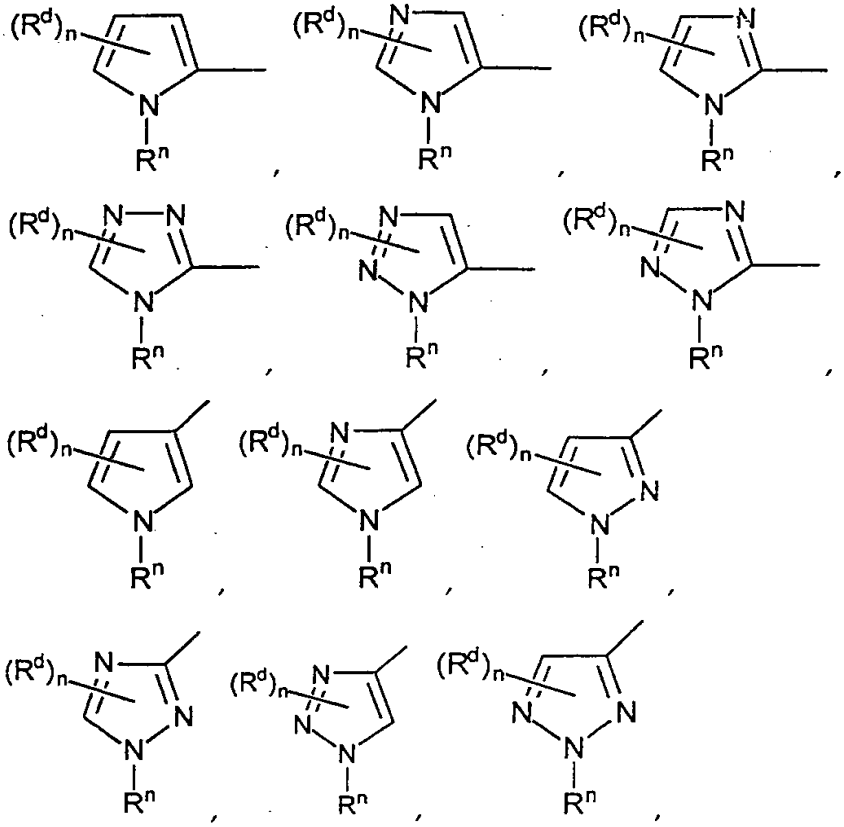


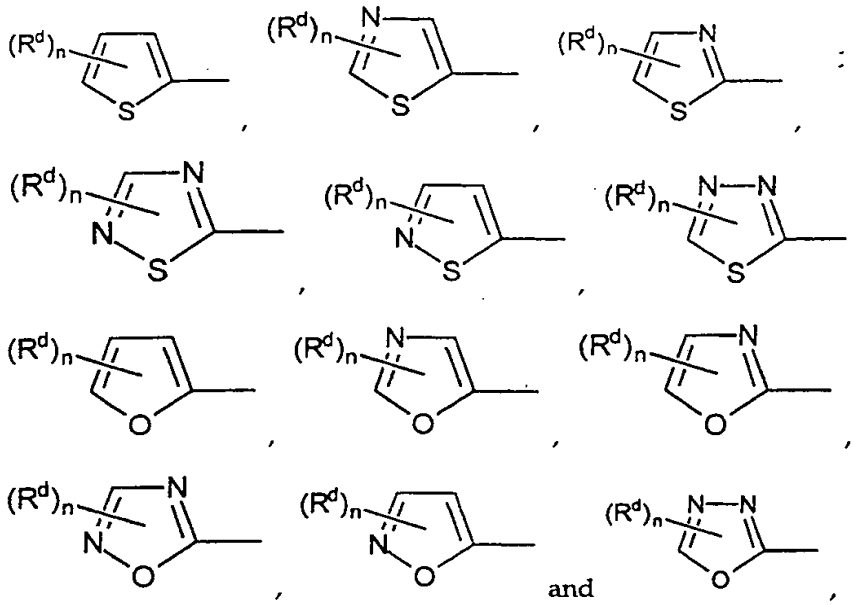
and

where Y^1, Y^2, Y^3, Y^4 and Y^5 are CH, CR^d or N, Z^1 is O, S, NH or NR^n and n is 0-3.

More specifically, D may be:

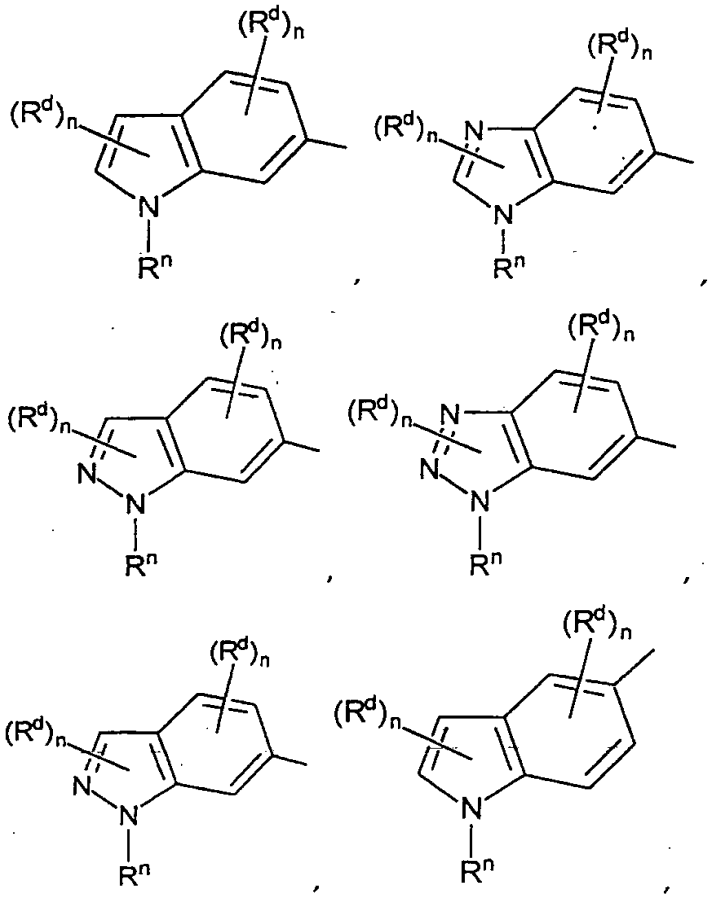
1) a 5-member aromatic heterocycle selected from;

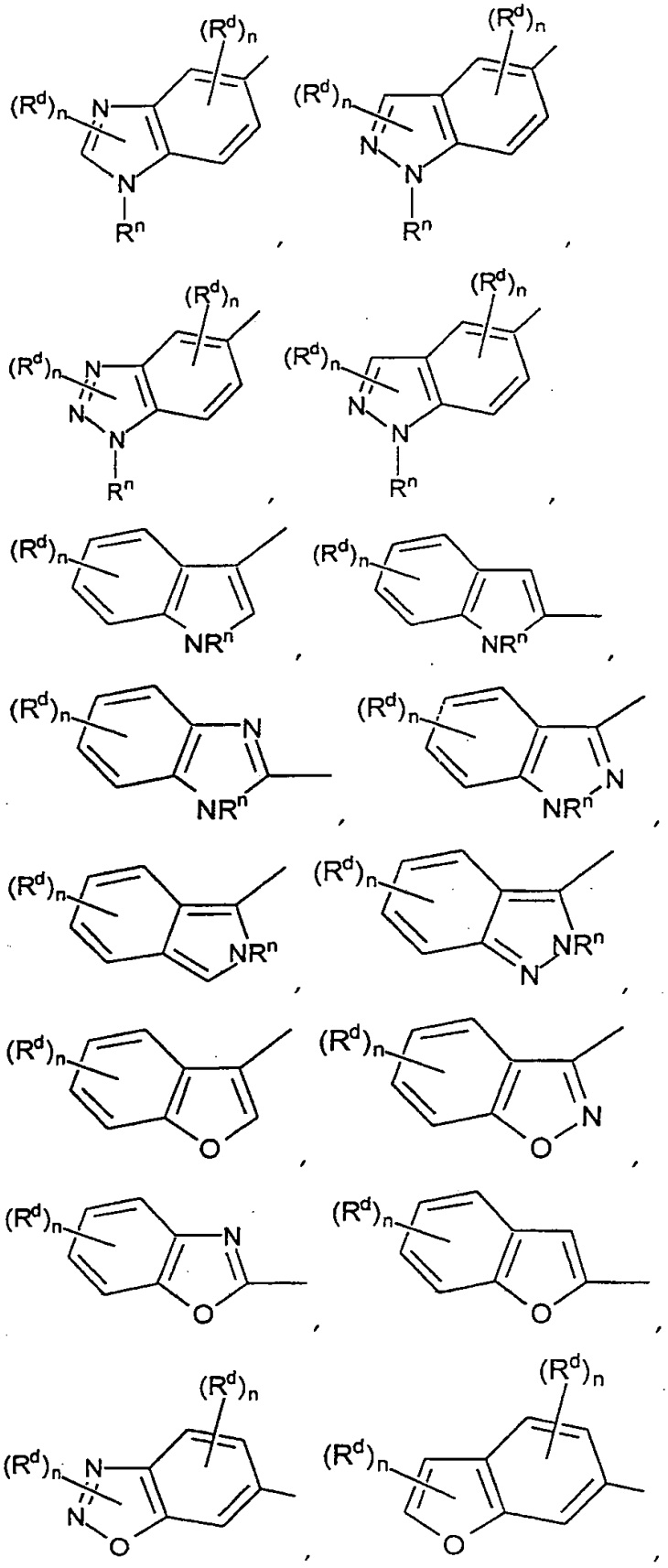


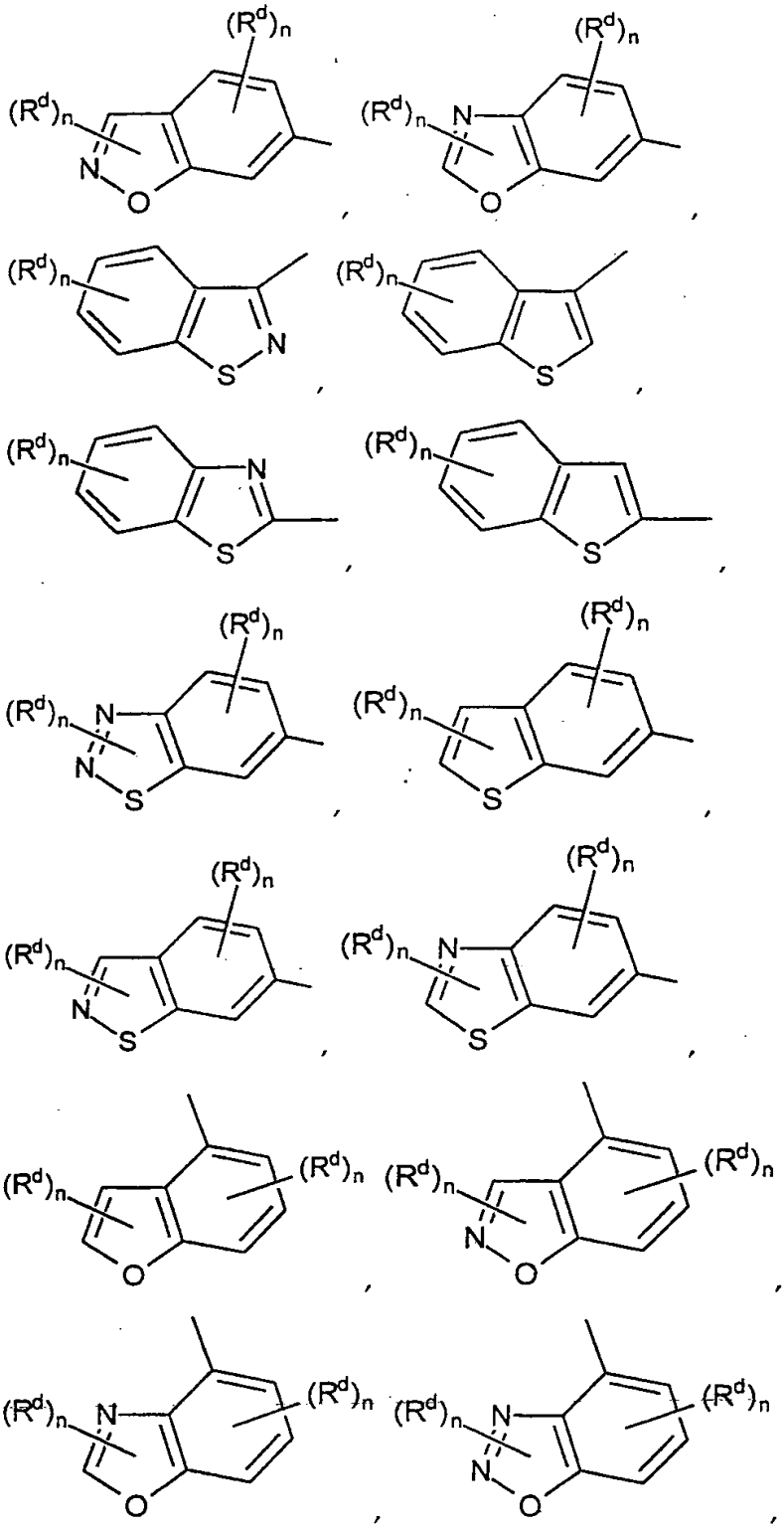


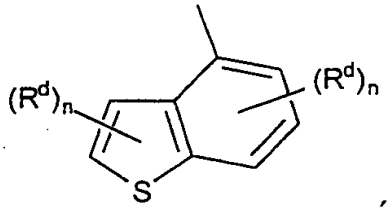
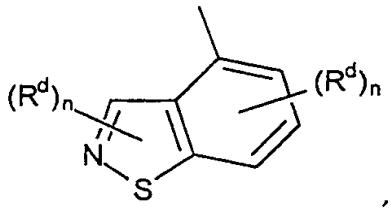
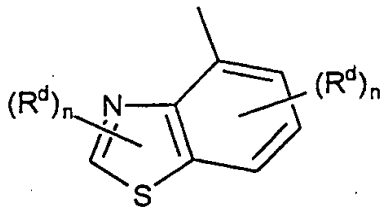
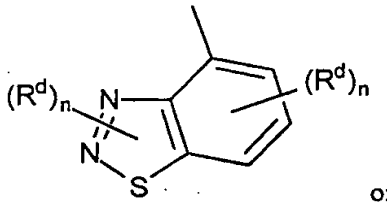
and

2) a 9-member aromatic heterobicycle selected from;



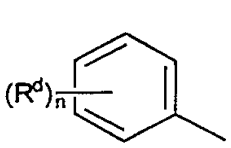
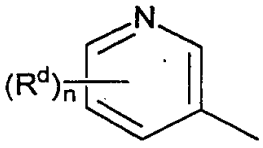
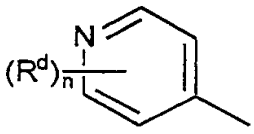




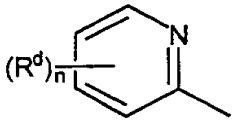





and or

3) a 6-member aromatic hetero- or homocycle selected from;

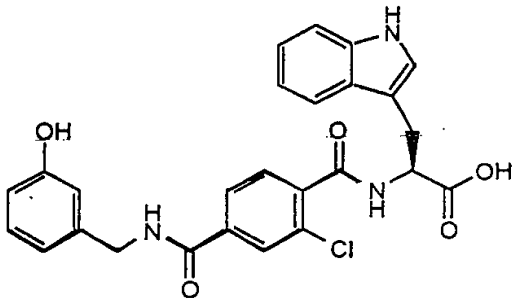
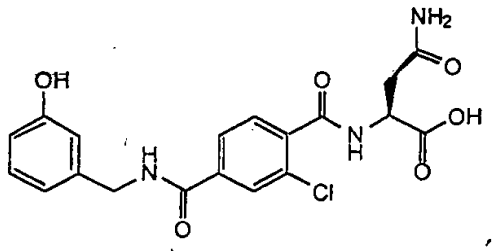
and

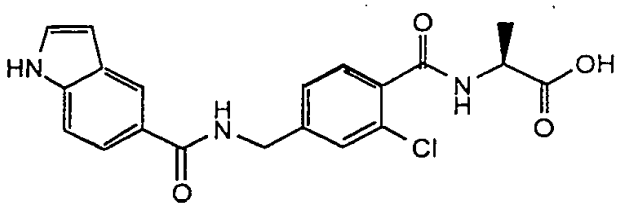


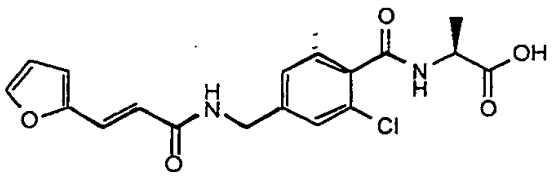
Compounds containing the foregoing preferred 5-member aromatic heterocycle and 9-member aromatic heterobicycle, 1 and 2 above, as aromatic groups D are preferred as LFA-1 specific antagonists, while the 6-member aromatic hetero- or homocycles of 3 above are preferred as D groups suitable for inhibiting both LFA-1 and Mac-1. In this latter case D is preferably substituted with a hydroxyl or precursor thereof.

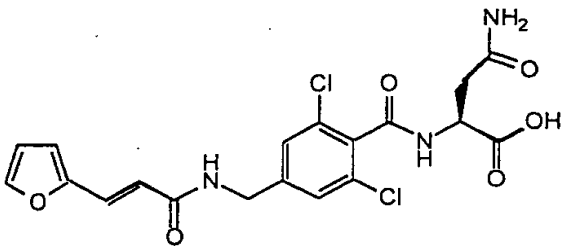
(h) Preferred substituents of D are one or more groups selected from; OH, NH_2, SO_2NH_2, SO_2CH_3, CH_3, CH_2OH, CN, CH_3-C(=O)NH-, $NH_2C(=O)$-, $NHCONH_2$, CF_3, C_1-C_6 alkoxy and halo(F, Cl, Br and I).

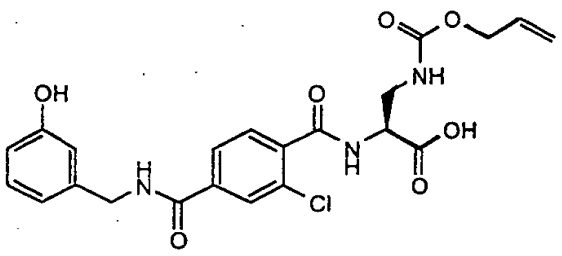
Exemplary preferred compounds of this invention include:

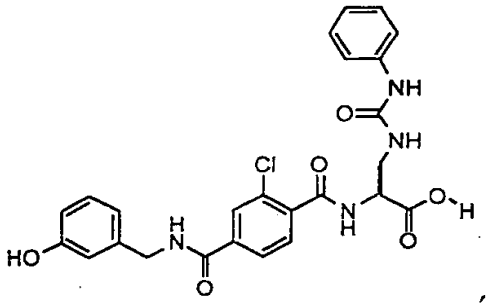



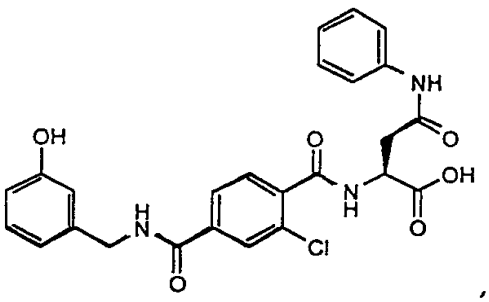


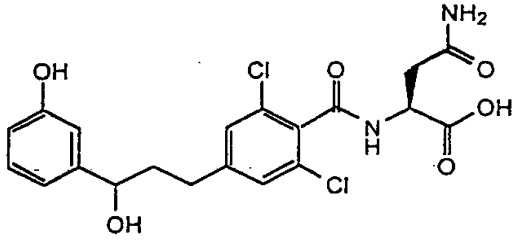


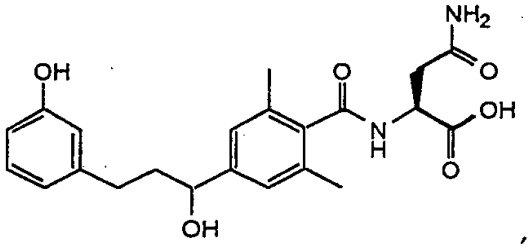


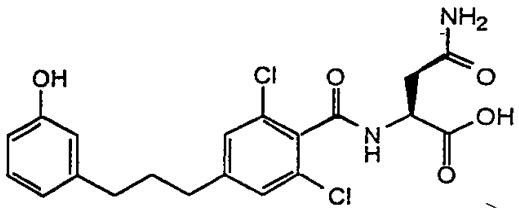


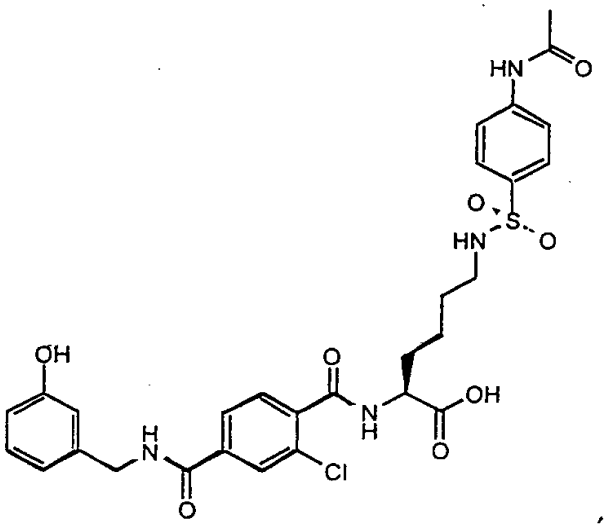


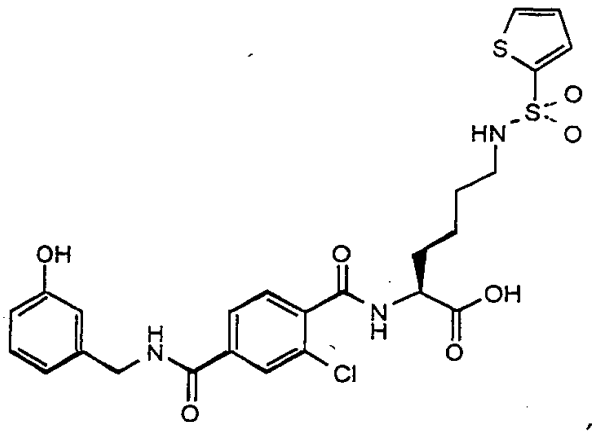


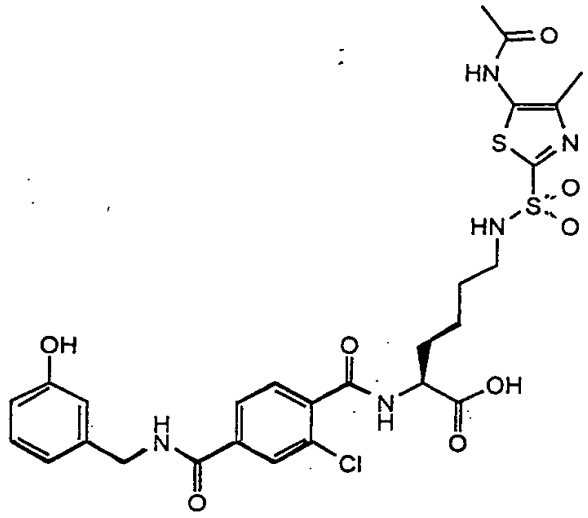


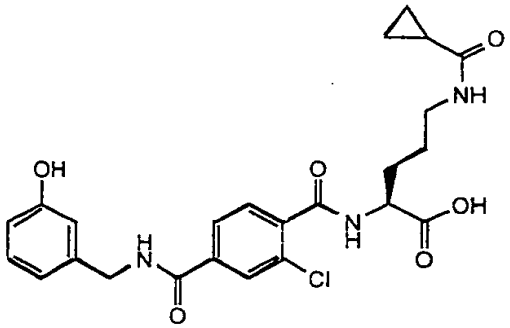


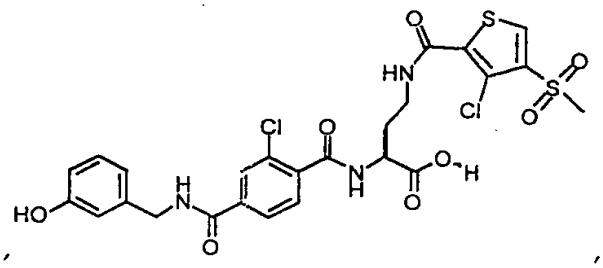


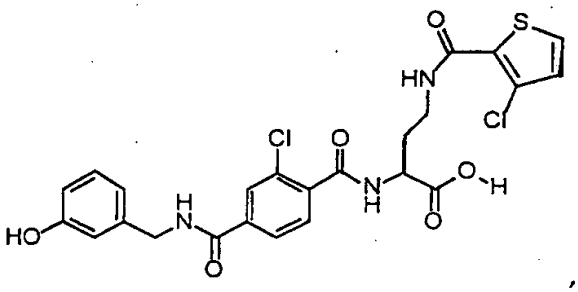


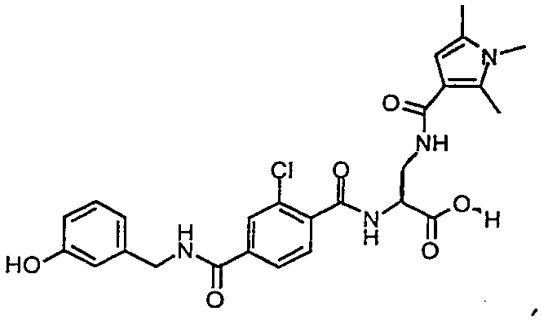


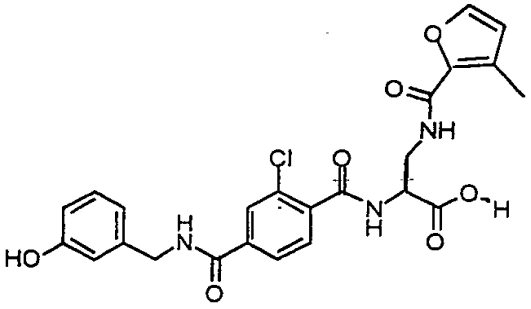


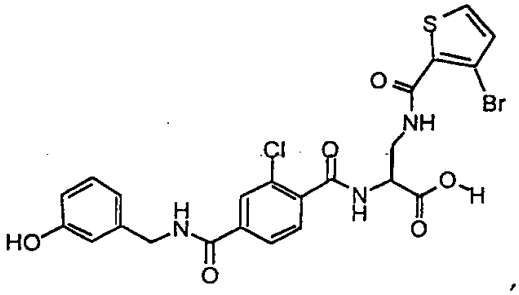


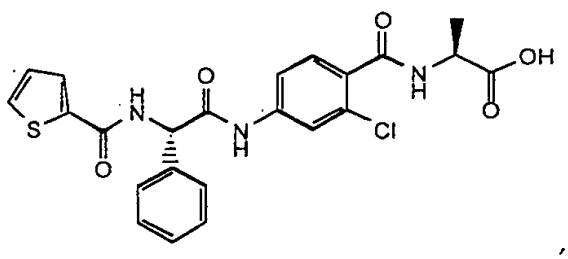


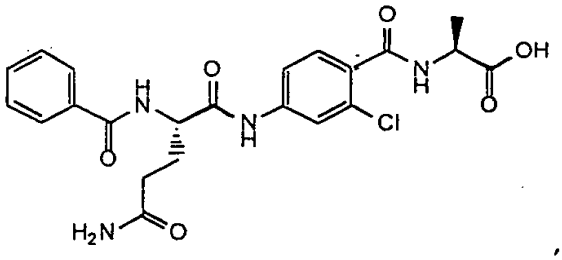


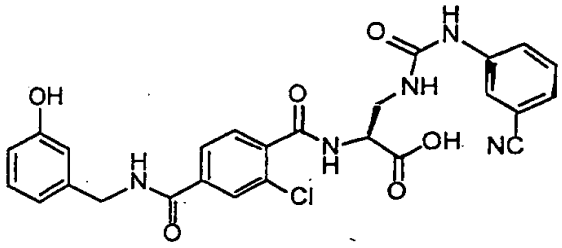


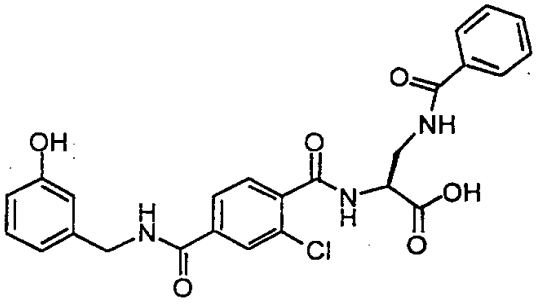


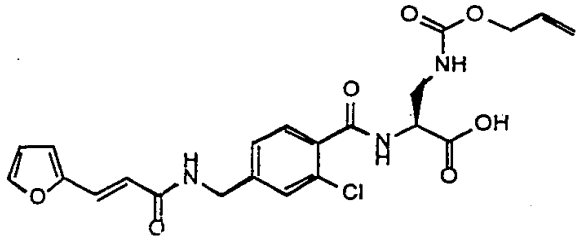


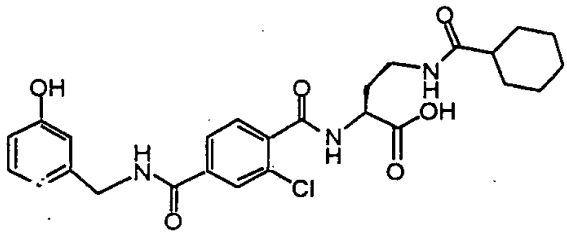


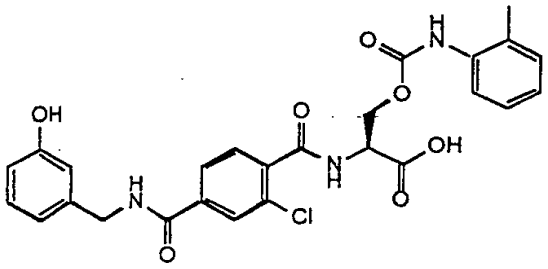


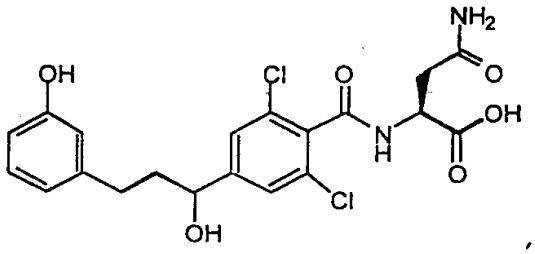


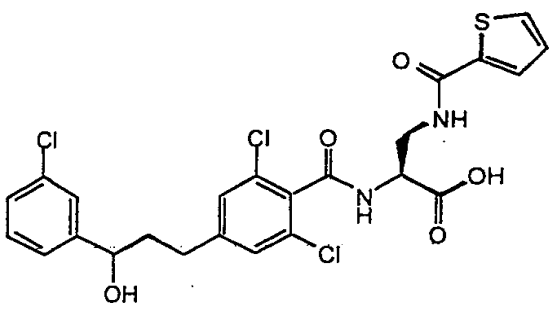


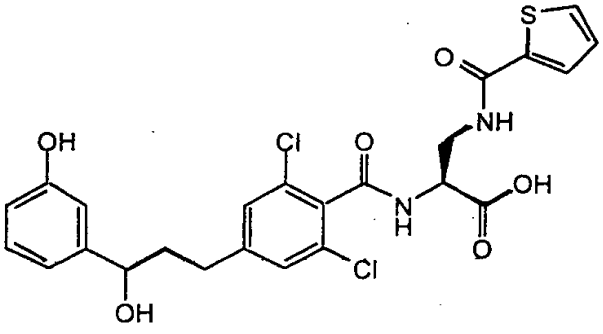












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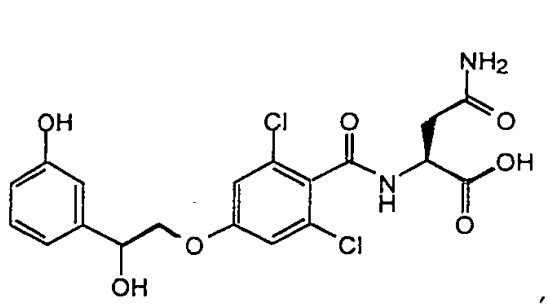
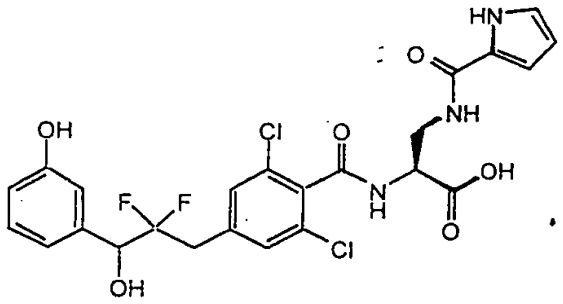
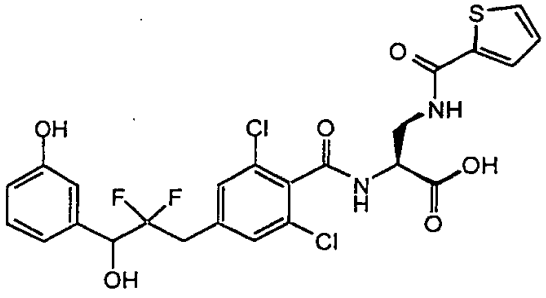
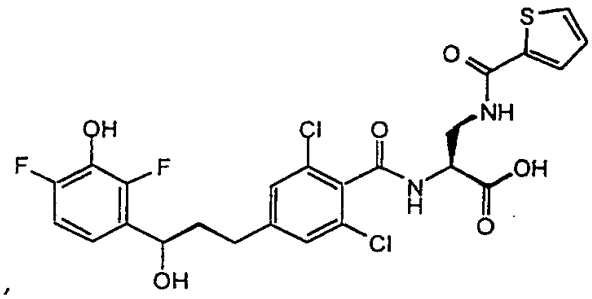
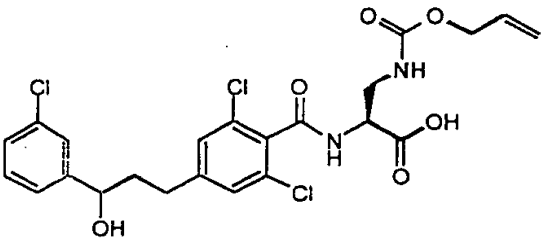
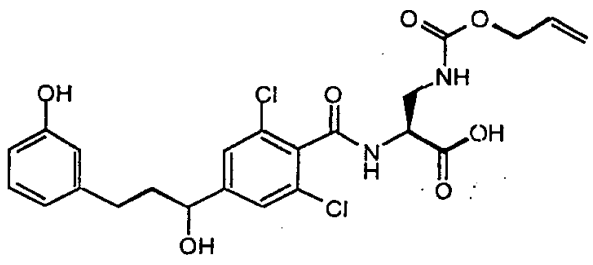


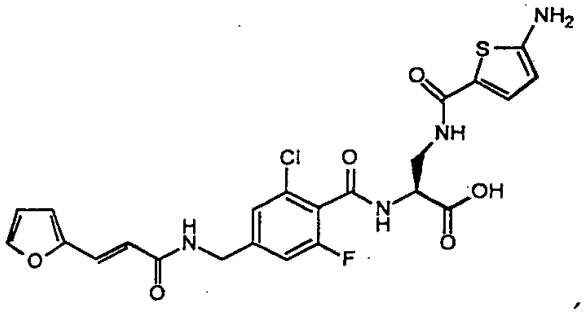


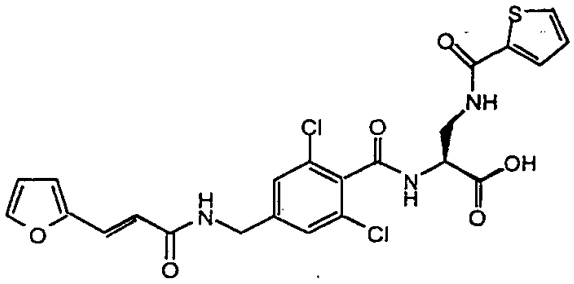


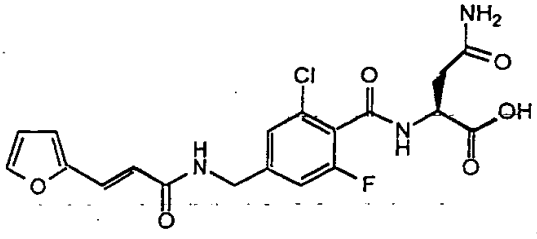




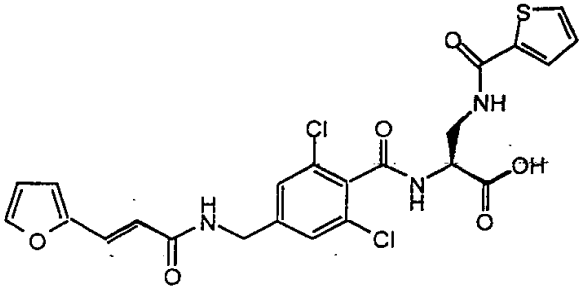








and



D Methods of Making

One method of producing LFA-1 antagonists involves chemical synthesis of the "peptide" or peptidomimetic. This can be accomplished using methodologies well known to those skilled in the

art (see Stewart and Young, *Solid Phase Peptide Synthesis* Pierce Chemical Co. Rockford, IL (1984); see also U. S. Patent No.'s 4,105,603; 3,972,859; 3,842,067; and 3,862,925)).

It will be appreciated from inspection of the compounds shown above that they all contain one or more amide or peptide bonds and thus may be considered peptidomimetics. Peptidomimetics of the invention may also be conveniently prepared using solid phase peptide synthesis (Merrifield, *J. Am. Chem. Soc.*, 85:2149 (1964); Houghten, *Proc. Natl. Acal. Sci. USA* 82:5132 (1985)). Solid phase synthesis begins at the carboxy-terminus of the putative peptide by coupling a protected amino acid to a suitable resin (*e.g.* chloromethylated polystyrene resin) as shown in Figures 1-1 and 1-2, on pages 2 and 4 of Stewart and Young *supra*. After removal of the α-amino protecting group with, for example, trifluoroacetic acid (TFA) in methylene chloride and neutralizing in, for example TEA, the next α-amino- and sidechain protected amino acid in the synthesis is added. The remaining α-amino- and, if necessary, side-chain-protected amino acids are then coupled sequentially in the desired order by condensation to obtain an intermediate compound connected to the resin. Alternatively, some amines and acids may be coupled to one another forming a peptide prior to addition of the peptide to the growing solid phase peptide chain.

The condensation between two amino acids can be carried out according to the usual condensation methods such as the azide method, mixed acid anhydride method, DCC (N,N'-dicyclohexylcarbodiimide) or DIPC (N,N'-diisopropylcarbodiimide)methods, active ester method (p-nitrophenyl ester method, BOP [benzotriazole-1-yl-oxy-tris (dimethylamino) phosphonium hexafluorophosphate] method, N-hydroxysuccinic acid imido ester method, etc., and Woodward reagent K method.

Common to chemical syntheses of peptides is the protection of any reactive side-chain groups of the amino acids with suitable protecting groups. Ultimately these protecting groups are removed after the desired polypeptide chain has been sequentially assembled. Also common is the protection of the α-amino group on an amino acid or a fragment while that entity reacts at the carboxyl group followed by the selective removal of the α-amino-protecting group to allow subsequent reaction to take place at that location. Accordingly, it is common in peptide synthesis that an intermediate compound is produced which contains each of the amino acid residues located in the desired sequence in the peptide chain with various of these residues having side-chain protecting groups attached. These protecting groups are then commonly removed substantially at the same time so as to produce the desired resultant product following removal from the resin.

Suitable protective groups for protecting the α-and ε- amino side chain groups are exemplified by benzyloxycarbonyl (CBZ), isonicotinyloxycarbonyl (iNOC), O-chlorobenzyloxycarbonyl (2-Cl-CBZ), p-nitrobenzyloxycarbonyl [Z(NO_2], p-methoxybenzyloxycarbonyl [Z(OMe)], t-butoxycarbonyl, (BOC), t-amyloxycarbonyl (AOC), isobornyloxycarbonyl, adamatyloxycarbonyl, 2-(4-biphenyl)-2-propyl-oxycarbonyl (BPOC), 9-fluorenylmethoxycarbonyl (FMOC), methylsulfo-nyiethoxycarbonyl (Msc), trifluoroacetyl, phthalyl,

formyl, 2-nitrophenylsulphenyl (NPS), diphenylphosphinothioyl (Ppt), dimethylophosphinothioyl (Mpt) and the like.

Protective groups for the carboxy functional group are exemplified by; benzyl ester (OBzl), cyclohexyl ester (Chx), 4-nitrobenzyl ester (ONb), t-butyl ester (OtBu), 4-pyridylmethyl ester (OPic), and the like. It is often desirable that specific amino acids such as arginine, cysteine, and serine possessing a functional group other than amino and carboxyl groups are protected by a suitable protective group. For example, the guanidino group of arginine may be protected with nitro, p-toluenesulfonyl, benzyloxycarbonyl, adamantyloxycarbonyl, p-methoxybenzenesulfonyl, 4-methoxy-2, 6-dimethylbenzenesulfonyl (Mds), 1,3,5-trimethylphenysulfonyl (Mts), and the like. The thiol group of cysteine may be protected with p-methoxybenzyl, triphenylmethyl, acetylaminomethyl ethylcarbamoyle, 4-methylbenzyl, 2, 4, 6-trimethy-benzyl (Tmb) etc., and the hydroxyl group of serine can be protected with benzyl, t-butyl, acetyl, tetrahydropyranyl and the like.

Stewart and Young *supra* provides detailed information regarding procedures for preparing peptides. Protection of α-amino groups is described on pages 14-18, and side-chain blockage is described on pages 18-28. A table of protecting groups for amine, hydroxyl and sulfhydryl functions is provided on pages 149-151.

After the desired amino acid sequence has been completed, the intermediate peptide is removed from the resin support by treatment with a reagent, such as liquid HF and one or more sulfur-containing scavengers, which not only cleaves the peptide from the resin, but also cleaves all the remaining side-chain protecting groups. Following HF cleavage, the peptide residue is washed with ether, and extracted from the resin by washing with aqueous acetonitrile and acetic acid.

Preferably in order to avoid alkylation of residues in the polypeptide, (for example, alkylation of methionine, cysteine, and tyrosine residues) a thio-cresol and cresol scavenger mixture is used.

Other General Procedures

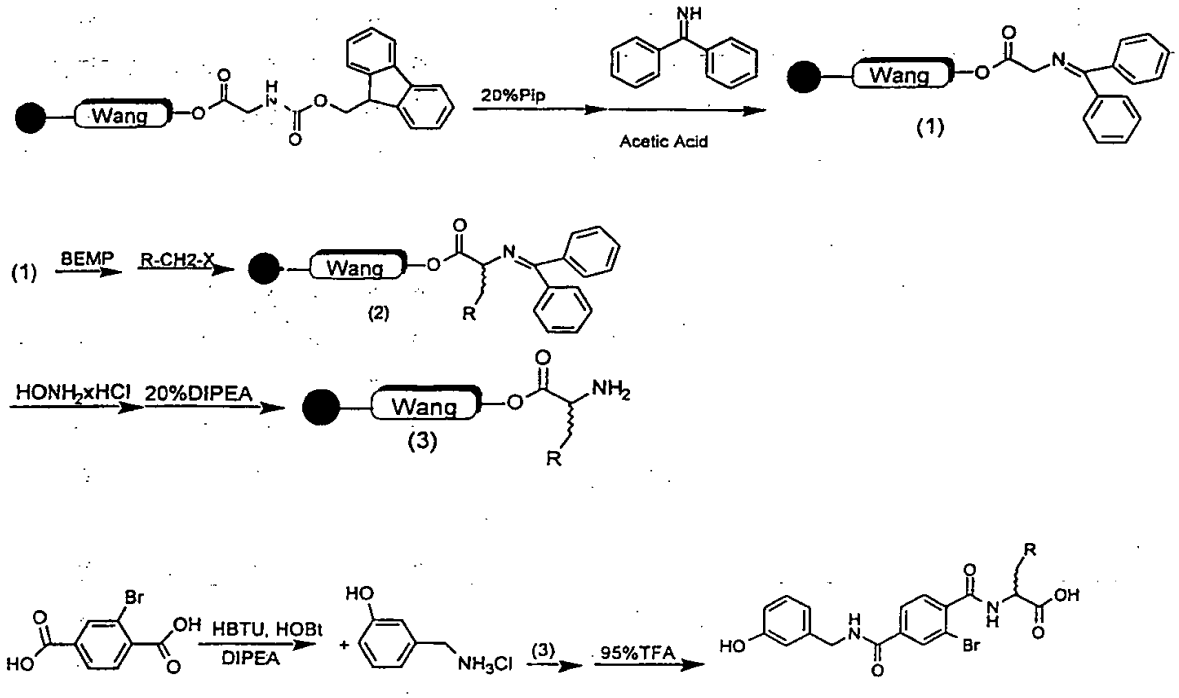
The peptidomimetic compounds of this invention may also be conveniently prepared by the methods for peptide synthesis described in monographs such as ("Principles of Peptide Synthesis, M. Bodanszky, Springer-Verlag, 2nd Ed., 1993; "Synthetic Peptides: A Users Guide", G. A. Grant, Ed, W. H. Freeman and Co., 1992; and references sited therein), or by other methods generally known to one skilled in the art. The synthesis of compounds of this invention that are peptidomimetic in nature (*i.e.* contain other than standard amide bond linkages between two or more amino acids) may be prepared by extension of the methods described in Examples 6 and by the general synthetic methods described in "Comprehensive Organic Transformations", R. C. Larock, VCH Publishers, 1989, and by methods generally known to one skilled in the art.

For compounds of Claim 1 where the amide linkages (-C(=O)-NH-) are replaced with amide isostere (Ai) linkages such as; (-C(=S)-NH-), (-S(=O)$_2$-NH-), -CH$_2$-NH-, -CH$_2$-S-, -CH$_2$-O-, -CH$_2$-CH$_2$-, -CH=CH- (cis and trans), -C(=O)-CH$_2$-, -CH(OH)-CH$_2$-, -CH(CN)-NH-, -O-C(=O)-NH-

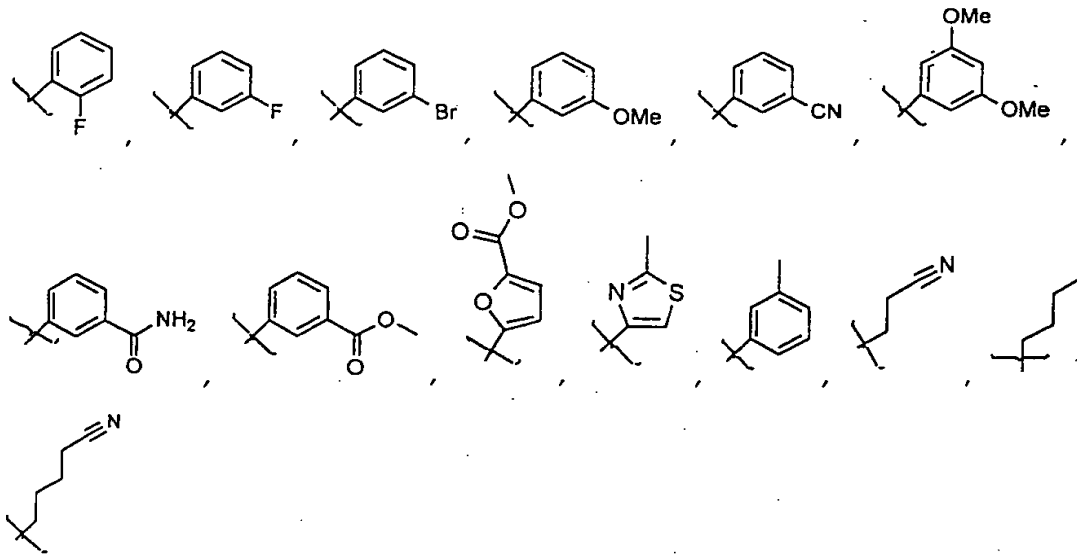
and -CH_2-SO-, amide bond replacing methods known in the art are employed. The following references describe preparation of amide isostere linkages which include these alternative-linking moieties: Spatola, A.F., Vega Data 1(3): "Peptide Backbone Modifications" (General Review) (Mar 1983), Spatola, A.F., in "Chemistry and biochemistry of Amino Acids Peptides and Proteins", B. Weinstein, ed., Marcel Dekker, New York, P. 267 (1983); Morley *Trends Pharm. Sci.* pp. 463-468; Hudson *et al. Int. J. Pept. Prot. Res.* 14:177-185 (1979) (-CH_2NH-, -CH_2CH_2-); Spatola *et al., Life Sci.* 38:1243-1249 (1986) (-CH_2-S-); Hann *J. Chem. Soc. Perkin. Trans. I* 307-314 (1982) (-CH=CH-, cis and trans); Almquist *et al., J. Med. Chem.* 23:1392-1398 (1980) (-C(=O)-CH_2-); Jennings-White *et al., Tetrahedron Lett* 23:(1982) (-C(=O)-CH_2-); Szelke *et al.*, EP Application No. 45665 (1982) *Chem Abs* :9739405 (1982) (-CH(OH)-CH_2); Holladay *et al., Tetrahedron Lett* 24:4401-4404 (1983) (-C(OH)-CH_2-); Hruby *Life Sci* 31:189-199 (1982) (-CH_2S-); Cho *et al., Science* 261:1303-1305 (1993) (-O-C(=O)-NH-); Sherman *et al., Biochem Biophys Res Comm* 162(3):1126-1132 (1989) (-C(=S)-NH-); Calcagni *et al., Int, J. Peptide Protein Res.* 34:319-324 (1989) (-S(=O)$_2$-NH-); TenBrink, *J. Org. Chem.* 52:418-422 (1987) -CH_2-O-.

Scheme I illustrates one synthetic approach which provides access to unnatural amino acid sidechains particularly for substituent T of Formula I. The method provides for α-alkylation of the "glycine" sidechain using a solid phase approach on a commercially available machine, such as an Argonaut Nautilus 2400.

Scheme I



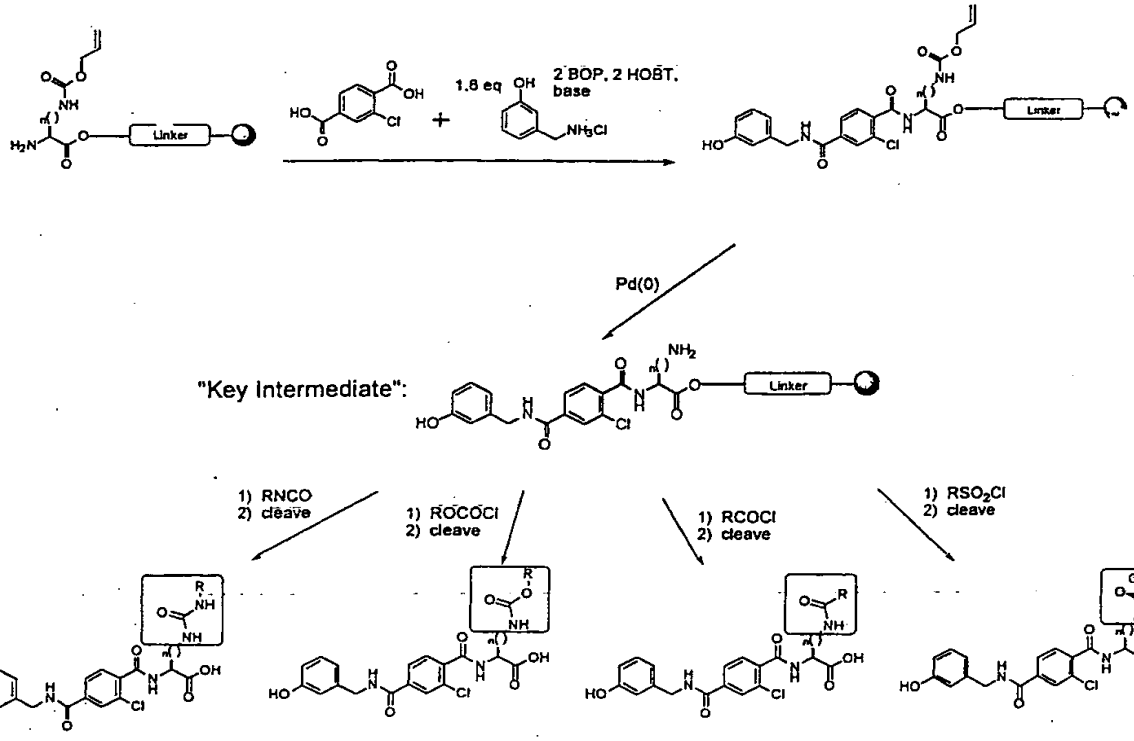
The following representative "R" groups can be introduced into the LFA-1 antagonists by the alkylation scheme above:



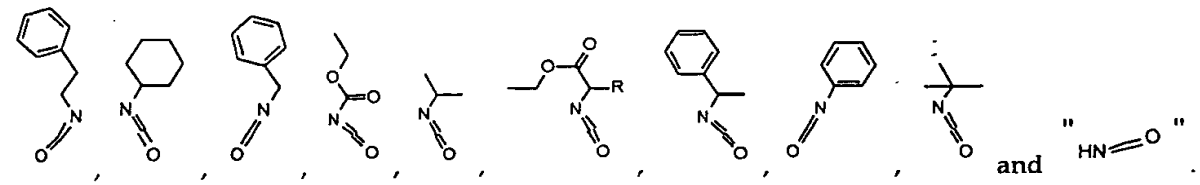
When "R" of Scheme I is an alkyl amine, prepared from the amino acids lys. orn or DAPA, reduction of the representative nitriles above or prepared from the protected (e.g. FMOC) aminoalkyl halide, synthetic routs are available to make derivatives of T including urea's, carbamates, amides and sulfonamides by known procedures.

Scheme II illustrates a solid phase approach for producing these derivatives of T.

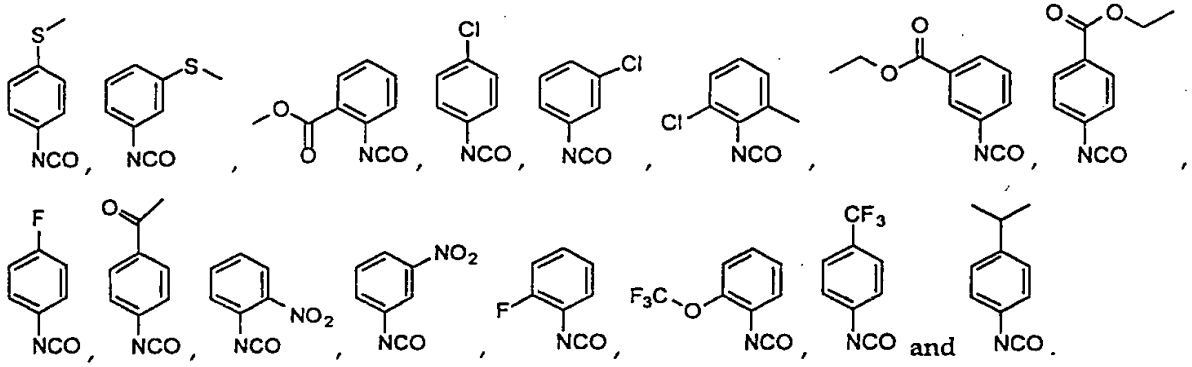
Scheme II



Urea's made according to Scheme II can be synthesized from representative commercially available isocyanates, RNCO's, including the following:

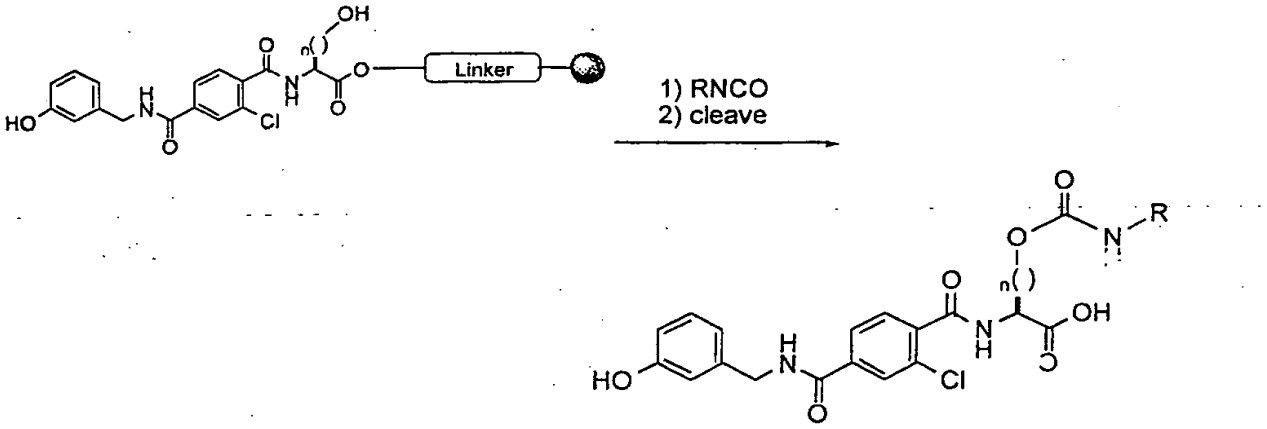


Other representative substituted aryl isocyanates suitable for use in the above scheme include:

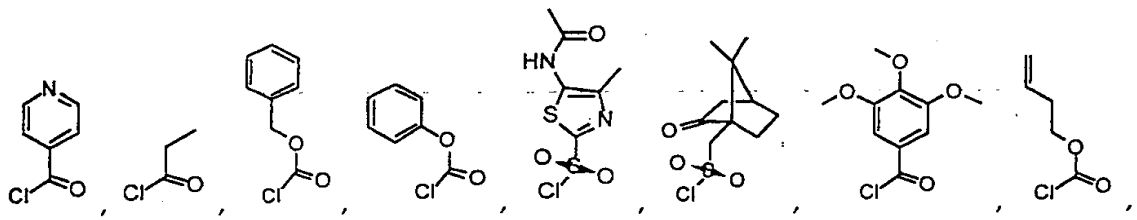


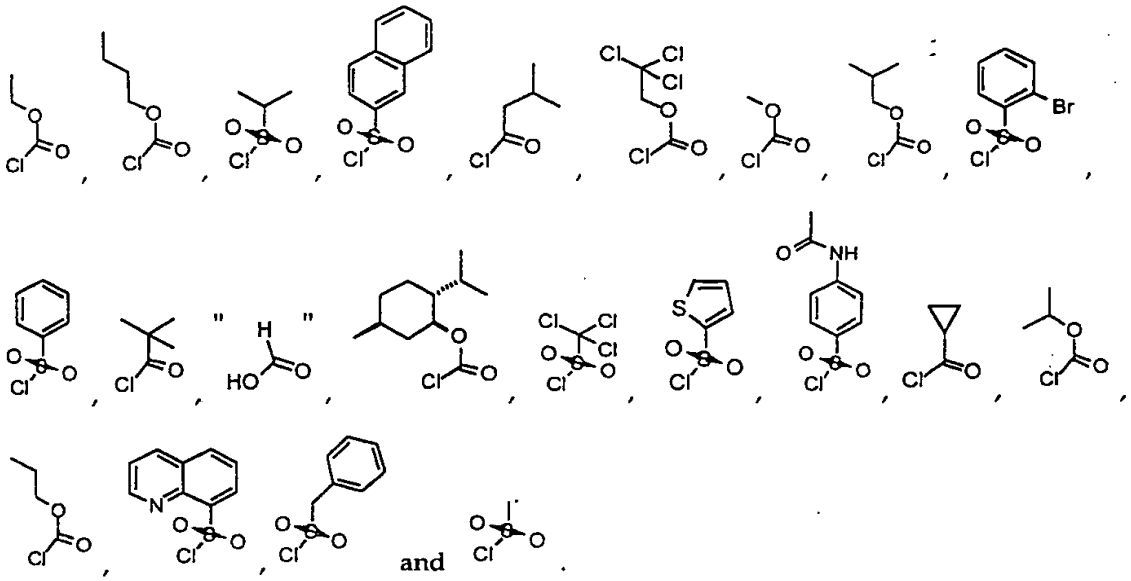
These and other isocyanates may be used to produce carbamates when the "R" in Scheme I is an alcohol (e.g. ser) according to scheme Scheme IIa below.

Scheme IIa



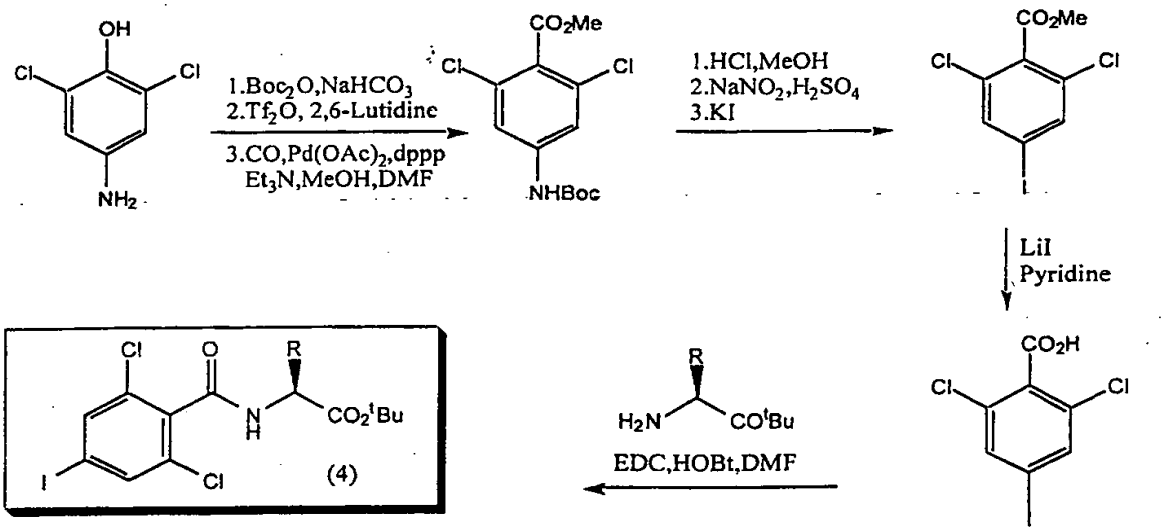
Carbamates (of the opposite orientation to Scheme IIa), amides and sulfonamides synthesized according to Scheme II can be made from representative commercially available ROCOCl's, RCOCl's and RSO_2Cl's including the following:





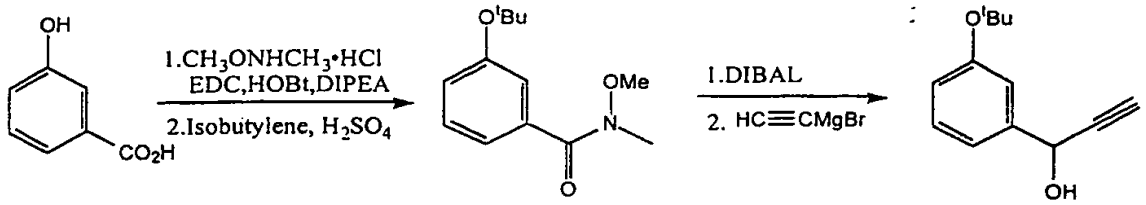
Scheme III illustrates a general synthetic route for alkyl linkers, L, for dichloro-substituted benzoyl-amino acids or derivitaves thereof. The key intermediate in this approach is the iodo, dichloro-benzoyl-AA (4).

Scheme III



Key intermediate (4) is coupled to a variety of alkynes to produce alkyl linkers of various length. For example a 3 carbon linker can be made by coupling (4) to alkyne intermediate (5) prepared according to Scheme IIIa.

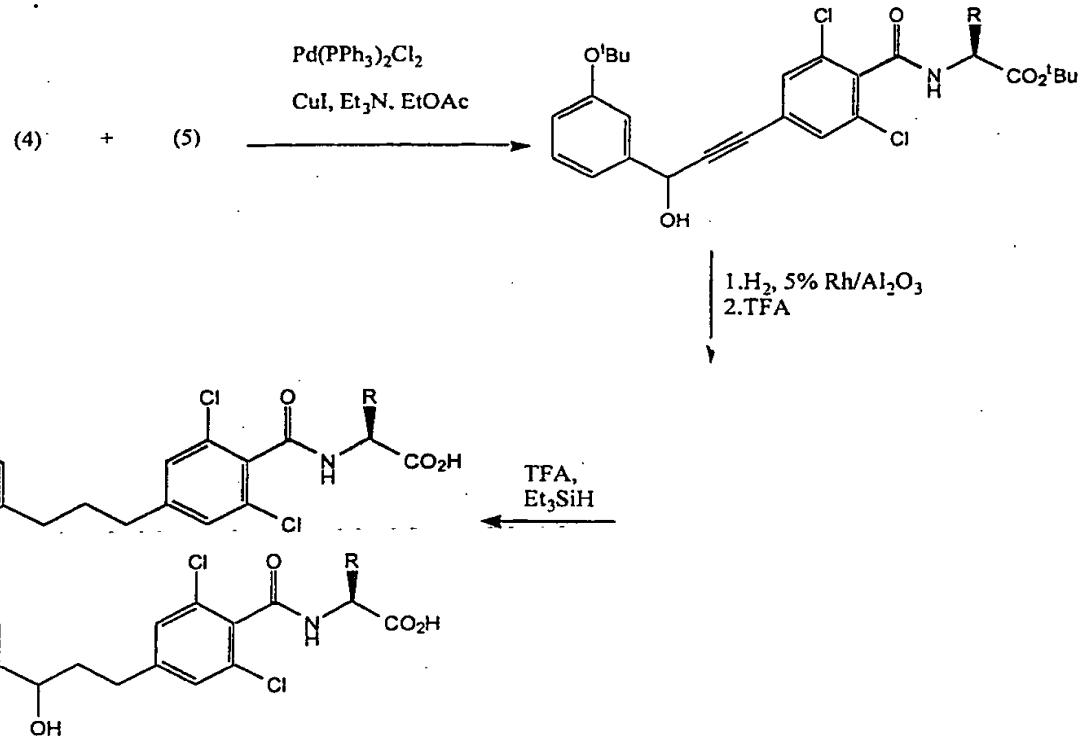
Scheme IIIa



(5)

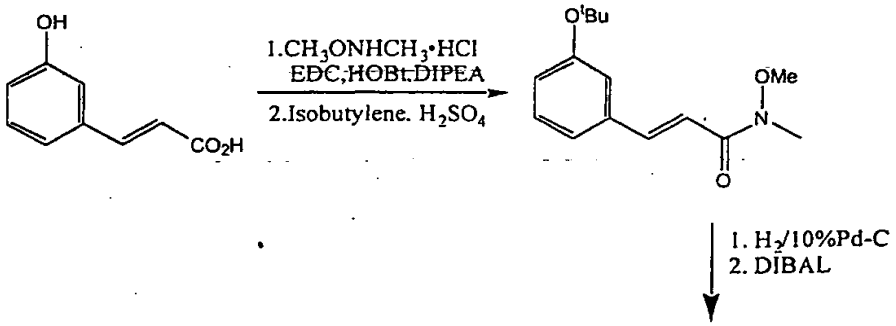
Scheme IV illustrates the synthesis of both substituted or unsubstituted alkane and substituted alkyne linkers.

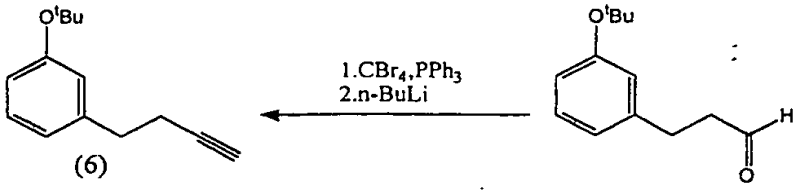
Scheme IV



A 4 carbon linker can be made by coupling (4) to alkyne intermediate (6) prepared according to Scheme V.

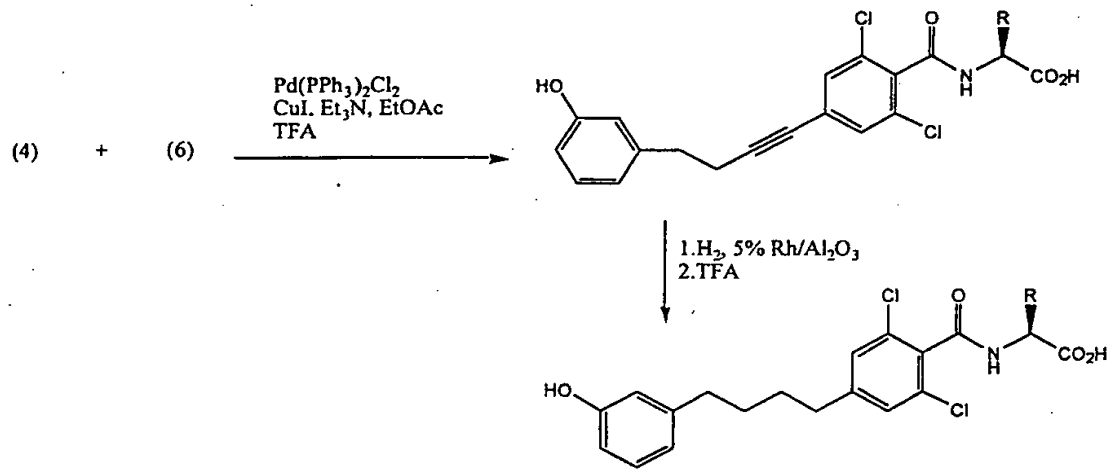
Scheme V





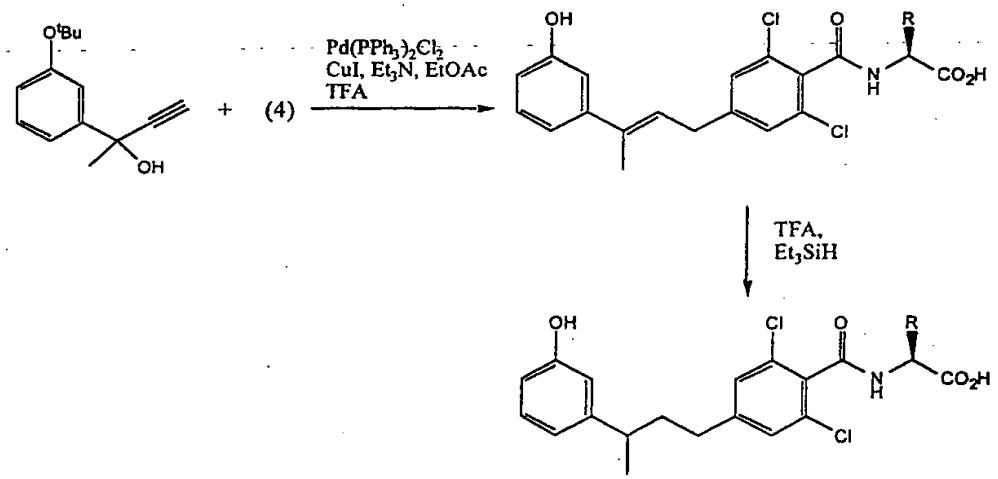
Scheme VI illustrates the synthesis of unsubstituted alkane and alkyne linkers.

Scheme VI

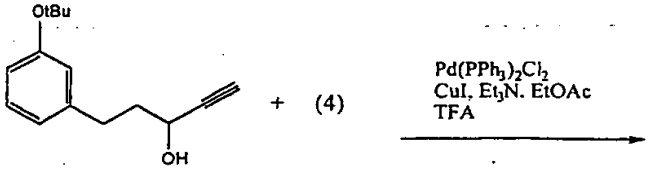


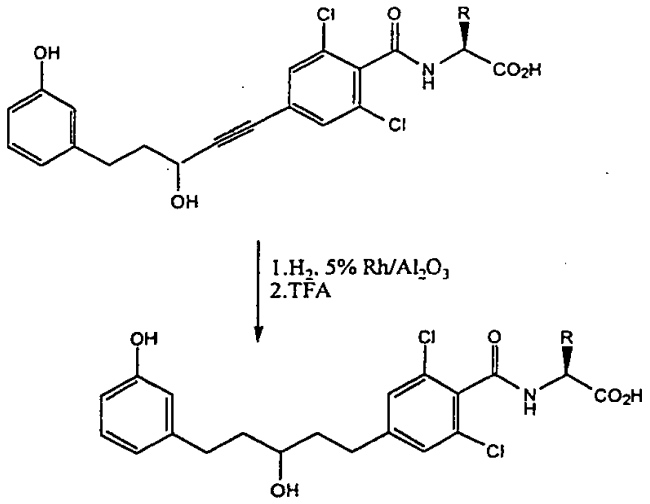
Schemes VIa and VIb illustrate the synthesis of substituted and unsubstituted alkane and alkene linkers of 3-5 carbons long.

Scheme VIa



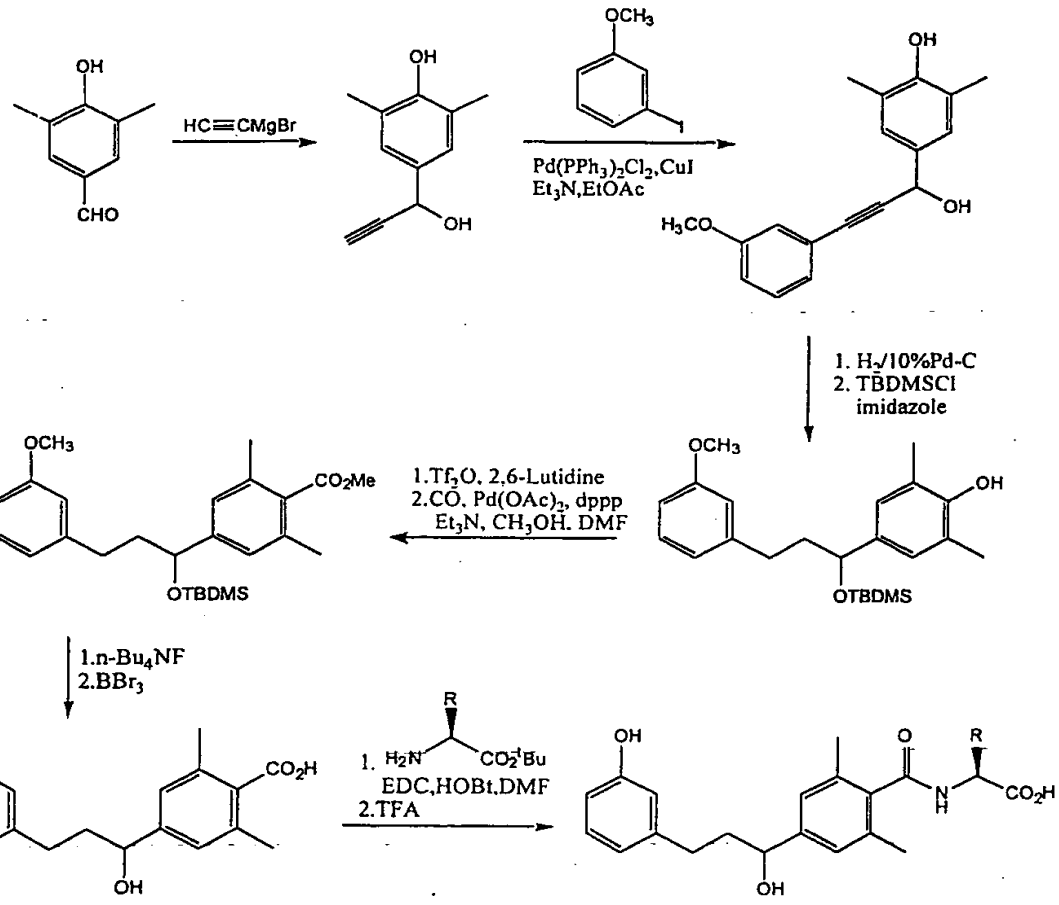
Scheme VIb





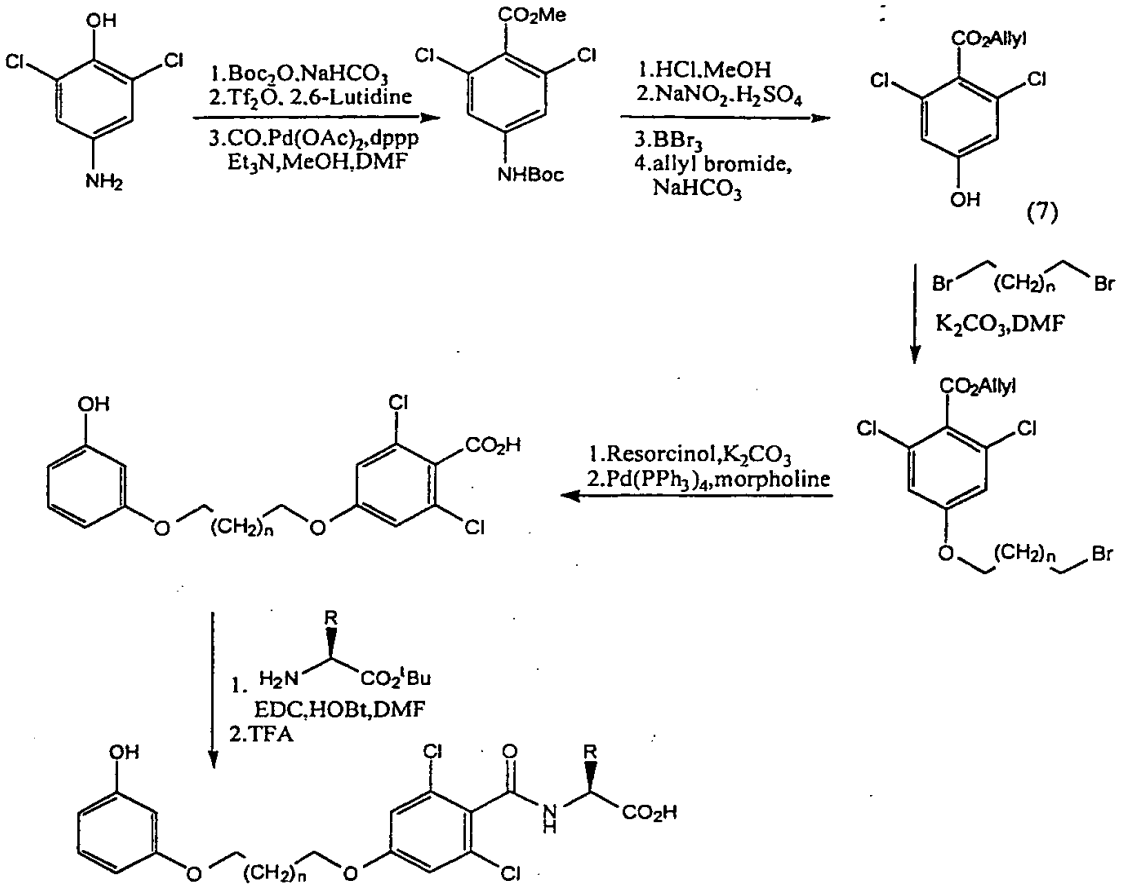
Scheme VII illustrates the synthesis of a 3-carbon alkyl linker where "B" is a dimethyl substituted benzoyl LFA-1 antagonist.

Scheme VII



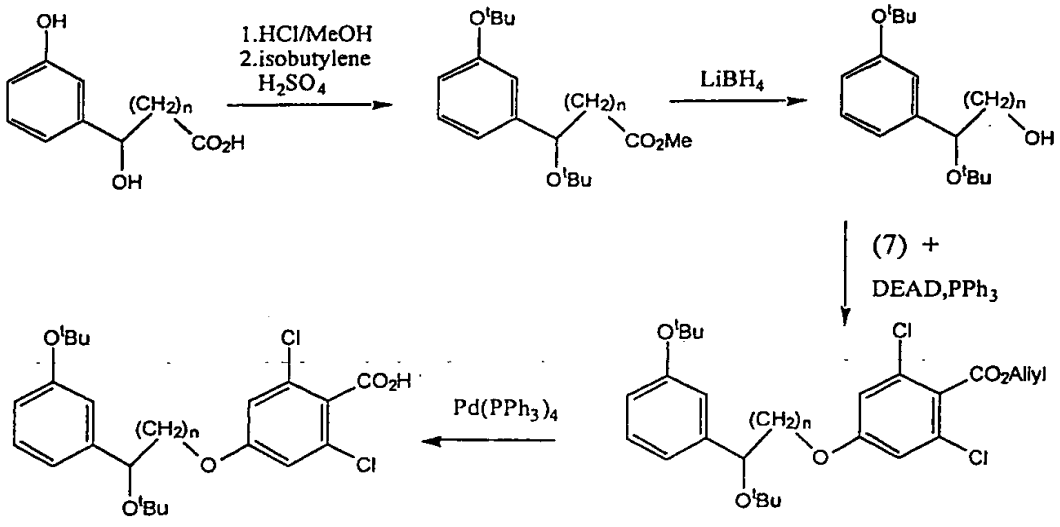
Scheme VIII illustrates the synthesis of a 3-5 atom diether linker where n is 1-3. Intermediate phenol (7) may also be used in the synthesis of monoethers described below.

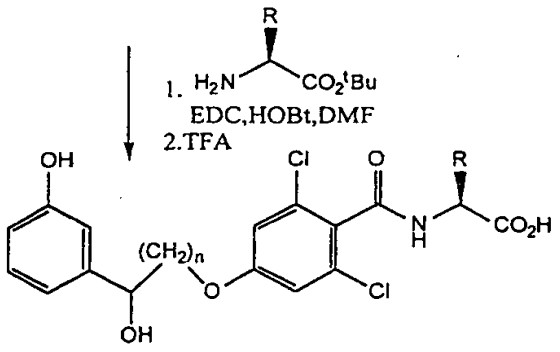
Scheme VIII



Scheme IX illustrates the synthesis of a 3-5 atom monoether linkers where n is 1-3. Intermediate phenol (7) above is employed in this method.

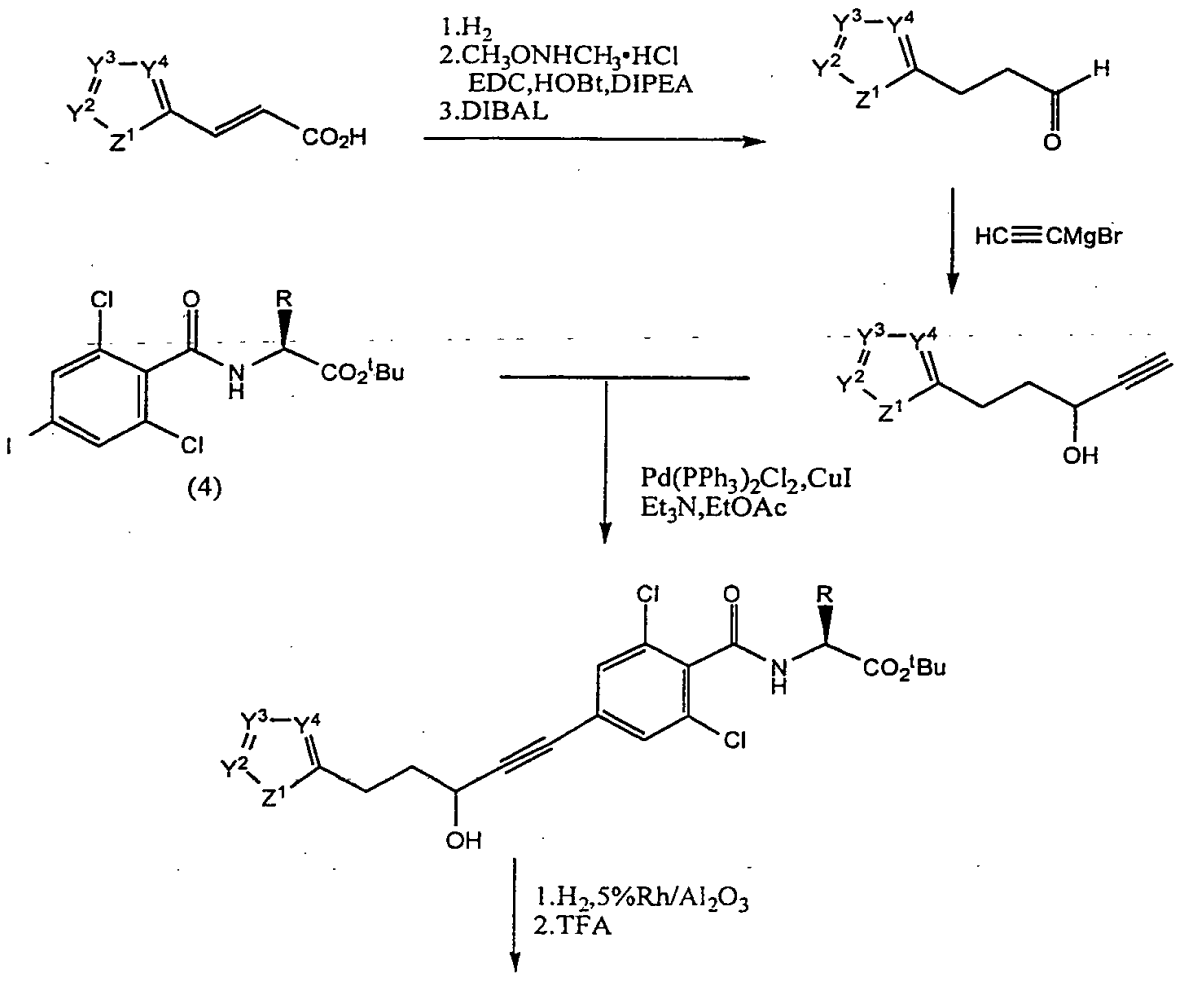
Scheme IX

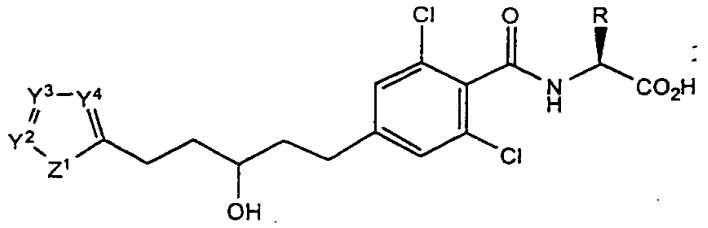




Scheme X illustrates the synthesis of a 5 atom alkyl linkers where the distyl group "D" is a 5-member aromatic ring. Preferred rings include thiophene, furan, thiazole and oxazole, where Z^1 is O or S and Y^2, Y^3 or Y^4 is selected from N or CH.

Scheme X

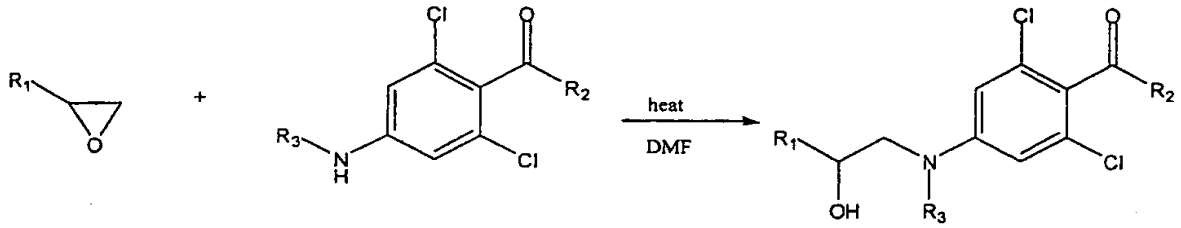




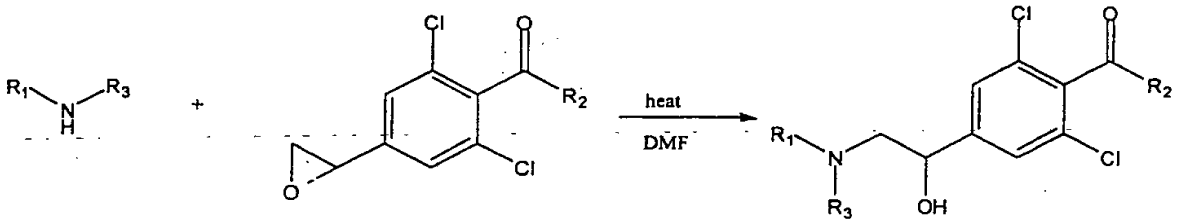
Scheme XI illustrates the synthesis of 3 atom aminoalcohol linkers where the distyl group "D" is phenyl or het.

Scheme XI

Beta hydroxy amines are produced via the reaction of a primary or secondary amine with epoxides. Epoxides are easily prepared by known methods (i.e. oxidation of alkenes).



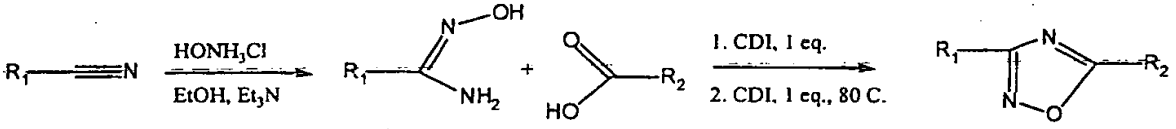
R1 = phenyl, alkyl, etc.
R2 = all possible C-termini
R3 = H or alkyl



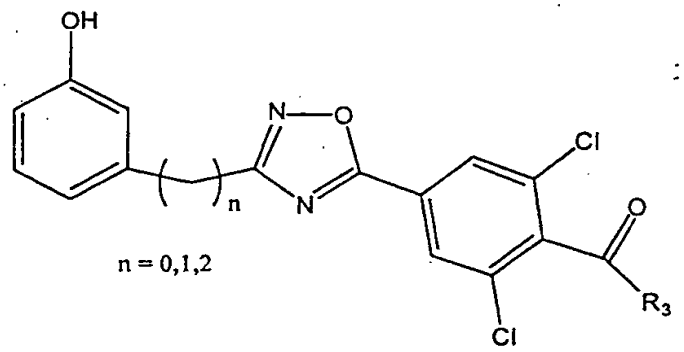
Scheme XII illustrates the synthesis of 3-5 atom oxadiazole linkers where the distyl group "D" is phenyl or het.

Scheme XII

Oxadiazoles are prepared from the combination of hydroxyamidine with an activated carboxylic acid under dehydrating conditions. Hydroxyamidines are conveniently prepared via reaction of a nitrile with hydroxylamine.



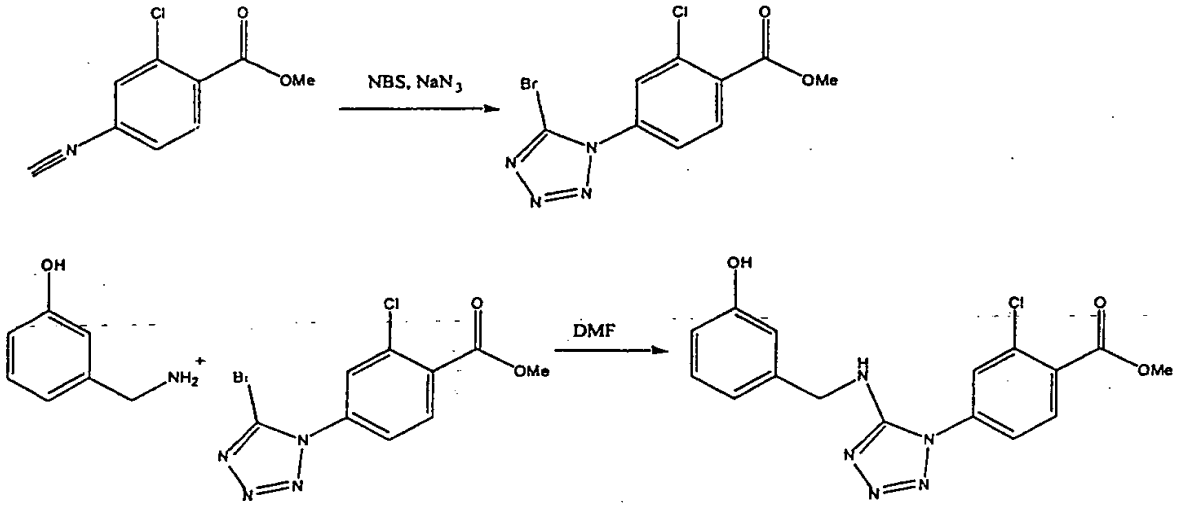
to prepare compounds such as:



Scheme XIII illustrates the synthesis of 5 atom aminotetrazoles linkers where the distyl group "D" is phenyl or het.

Scheme XIII

The key step in the preparation of aminotetrazoles is the reaction of a 5-halo-1-phenyltetrazole with an amine. Aminotetrazoles are formed from the reaction of N-bromosuccinimide and sodium azide with phenylisocyanide under phase transfer conditions.



Deprotection and coupling at the carboxylate to add the left side amino acid is carried out as described previously for other compounds.

E. Modes for Carrying Out the Invention

Superior immunosuppressive efficacy is seen with a treatment regimen that uses early induction with a high dose of LFA-1 antagonist followed by extended treatment with a lower dose of antagonist.

Typically, the LFA-1 antagonist used in the method of this invention is formulated by mixing it at ambient temperature at the appropriate pH, and at the desired degree of purity, with physiologically acceptable carriers, i.e., carriers that are non-toxic to recipients at the dosages and concentrations employed. The pH of the formulation depends mainly on the particular use and the concentration of antagonist, but preferably ranges anywhere from about 3 to about 8. Formulation in an acetate buffer at pH 5 is a suitable embodiment.

The LFA-1 antagonist for use herein is preferably sterile. LFA-1 antagonist ordinarily will be stored as a solid composition, although lyophilized formulations or aquous solutions are acceptable.

The antagonist composition will be formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The "therapeutically effective amount" of LFA-1 antagonist to be administered will be governed by such considerations, and is the minimum amount necessary to prevent, ameliorate, or treat the LFA-1-mediated disorder, including treating rheumatoid arthritis, multiple sclerosis, asthma, psoriasis (topically or systemically), reducing inflammatory responses, inducing tolerance of immunostimulants, preventing an immune response that would result in rejection of a graft by a host or vice-versa, or prolonging survival of a transplanted graft. Such amount is preferably below the amount that is toxic to the host or renders the host significantly more susceptible to infections.

As a general proposition, the initial pharmaceutically effective amount of the LFA-1 antagonist administered parenterally per dose will be in the range of about 0.1 to 20 mg/kg of patient body weight per day, with the typical initial range of LFA-1 antagonist used being 0.3 to 15 mg/kg/day.

The LFA-1 antagonist is administered by any suitable means, including oral, topical, transdermal, parenteral, subcutaneous, intraperitoneal, intrapulmonary, and intranasal, and, if desired for local immunosuppressive treatment, intralesional administration (including perfusing or otherwise contacting the graft with the antagonist before transplantation). Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration. A preferred administration method for psoriasis is topical in close proximity to the affected area.

The LFA-1 antagonist need not be, but is optionally formulated with one or more agents currently used to prevent or treat the disorder in question. For example, in rheumatoid arthritis, the LFA-1 antagonist may be given in conjunction with a glucocorticosteroid. In addition, T-cell receptor peptide therapy is suitably an adjunct therapy to prevent clinical signs of autoimmune encephalomyelitis (Offner *et al., supra.*). For transplants, the LFA-1 antagonist may be administered concurrently with or separate from an immunosuppressive agent as defined above, e.g., cyclosporin A, to modulate the immunosuppressant effect. The effective amount of such other agents depends on the amount of LFA-1 antagonist present in the formulation, the type of disorder or treatment, and other factors discussed above.

The various autoimmune disorders described above are treated with LFA-1 antagonists in such a fashion as to induce immune tolerance to the self antigen under attack as a result of the disorder. In this regard, autoimmune disorders resemble host versus graft rejection and are treated with LFA-1 antagonists in analogous fashion. However, in these disorders the patient is

already mounting an immune response to the target antigen, unlike the case with transplants prior to grafting. Thus, it is desirable to first induce and maintain a transient state of immunosuppression by conventional methods in such patients, e.g. by the conventional use of cyclosporin A or other conventional immunosuppressive agents (alone or together with LFA-1 antagonist), or to monitor the patient until the occurrence of a period of remission (an absence or substantial lessening of pathological or functional indicia of the autoimmune response).

The invention will be more fully understood by reference to the following examples. They should not, however, be construed as limiting the scope of the invention. All literature citations are incorporated by reference.

Examples

Example 1

Preparation and Purification of full-length LFA-1 from 293 Cells

Construction of LFA-1 cDNA expression vector

A plasmid with both the human CD11a (α_L) and CD18 (β_2) sequences, each with a separate CMV promoter for expression in 293 cells, was constructed as follows. The plasmid, pRKCD18, containing the full length CD18 cDNA, was cut with restriction enzymes HpaI and Avr II. The plasmid, pRKCD11a, containing the full length CD11a cDNA, was treated with the enzyme Taq I methylase to methylate one of the two Xmn I sites, then cut with Xmn I and Spe I. The fragment from the pRKCD18 digest containing the CD18 coding sequence, the CMV promoter, the antibiotic resistance gene and other plasmid sequences was ligated to the fragment from the pRKCD11a digest containing the CD11a coding sequence and the CMV promoter. The Spe I and Avr II sticky ends are compatible and were ligated together. The Hpa I and Xmn I ends are both blunt and were ligated together to generate the pRK LFA a+b plasmid.

Generation of LFA-1 expressing 293 cell line

A cell line expressing human LFA-1 was generated by cotransfecting 293 cells with a plasmid (pRK LFA a+b) containing the full-length cDNAs for the aL (CD11a) and b2 (CD18) subunits together with pRSVneo, which encodes the G418 resistance marker under the control of the RSV promoter, using previously described methods. (Bodary, Napier and McLean, J Biol. Chem, 264, 32, 18859-18862, 1989). Upon growth in the presence of 0.8mg/ml of G418 for 20 days a population of drug resistant cells was selected for LFA-1 expression, using two color FACS (fluoresence activated cell sorting,) with monoclonal antibodies directed against the a L subunit (Fluorescein isothiocyanate labeled monoclonal antibody clone 25.3, catalogue # 0860, AMAC, Inc.) or the b2 subunit-complex (Phycoerythrin labeled MHM23.) (MHM23 antibody reference: Hildreth JEK, and August JT, J Immunol, 134, 3272-3280, 1985) After three rounds of FACS a clonal population was isolated (clone 19) and receptor number was determined to be approximately 106 LFA-1 per cell by Scatchard analysis. This cell line was grown under serum free suspension culture conditions to generate cell pellets for the purification of LFA-1.

Cell Extraction (All procedures are at 0-4 ° C.)

The frozen 293 cell pellet was suspended in 5 volumes of 0.3 M sucrose/20 mM HEPES/5 mM $CaCl_2$/5 mM $MgCl_2$/2 mg/ml aprotinin pH 7.4 using a Polytron homogenizer (Brinkman) at approximately 8000 rpm. Once a uniform suspension was obtained, the cells were homogenized at approximately 20,000 rpm for 1 min. Phenylmethane sulfonyl fluoride (PMSF, 100 mM in isopropanol) was then added to the homogenate to a final concentration of 1 mM, and the homogenate was centrifuged at 21,000 x g for 40 min. The supernatant was discarded and the pellet suspended in a volume of 1% Triton X-100 (ultrapure)/0.15 M NaCl/20 mM HEPES/5 mM $CaCl_2$/5 mM $MgCl_2$/20 mg/ml aprotinin/1 mM PMSF pH 7.4 equal to the volume of sucrose buffer above. The cells were homogenized briefly at about 8000 rpm with the Polytron then placed on a rocker for 30 min. The extract was centrifuged as above and the supernatant saved.

Lentil Lectin Column

Approximately 3 to 4 column volumes of cell extract were loaded at 15 cm/hr onto a lentil lectin Sepharose column (Pharmacia) equilibrated in 0.1% Triton X-100/0.15 M NaCl/20 mM HEPES/5 mM $CaCl_2$/5 mM $MgCl_2$ pH 7.4. Once the sample was loaded, the column was washed with equilibration buffer until the $A_{280\ nm}$ reached baseline. LFA-1 was eluted with 0.5 M a-methyl mannoside in equilibration buffer. To maximize recovery, elution was stopped when the LFA-1 started to appear, the column was left overnight in elution buffer then elution was resumed.

Q Sepharose Column

The lentil eluate was diluted with an equal volume of 0.1% Triton X-100/20 mM HEPES/5 mM $CaCl_2$/5 mM $MgCl_2$ pH 7.4 and loaded at 15 cm/hr onto a Q Sepharose High Performance column (Pharmacia) equilibrated in the same buffer. After the sample was loaded, the column was washed with equilibration buffer until the $A_{280\ nm}$ approached baseline, then with 1% octyl glucoside/20 mM HEPES/5 mM $CaCl_2$/5 mM $MgCl_2$ pH 7.4 until the Triton X-100 was removed. The LFA-1 was eluted with a 10 column volume 0 to 0.3 M NaCl gradient in the same buffer. Fractions were analyzed by SDS PAGE and the peak fractions pooled and stored frozen at -70□ C.

Example 2

ICAM-1-immunoadhesin

Plasmid for expression of a human ICAM-1-immunoadhesin

A plasmid for the expression of a human ICAM-1 immunoadhesin was constructed and named pRK.5dICAMGaIg. This plasmid contains; a CMV (cytomegalovirus) promoter and enhancer region, an SP6 promoter for making riboprobes, the five immunoglobulin-like domains of ICAM-1, a six amino acid cleavage site recognized by Genenase (a genetically engineered form of subtilisin), the Fc region from human IgG, an SV40 early polyadenylation site, an SV40 origin of replication, a bacterial origin of replication, and a bacterial gene coding for ampicillin resistance.

This plasmid was constructed using fragments from two other plasmids. The first plasmid, pRKICAMm.2, is a plasmid for the expression of full-length ICAM-1. The following two primers were used to generate a fragment containing the five immunoglobulin-like domains of ICAM-1 by

PCR : 1) a 17bp forward primer which is homologous to a portion of the vector sequence 5' of the ICAM-1 coding sequence -5' TGC CTT TCT CTC CAC AG 3' and 2) a 48bp reverse primer which is homologous to 7 amino acids at the 3' end of Ig-like domain 5 and contains sequence coding for a protease cleavage site - 5' GG TGG GCA CAG AGT GTA GTG CGC AGC CTC ATA CCG GGG GGA GAG CAC A 3'. The PCR reaction used 0.2μg of pRKICAMm.2, 1 μl forward primer, at 10 OD/ml, 2μl reverse primer, at 10 OD/ml, 0.2 mM each dATP, dCTP, dGTP, and dTTP, 0.5 mM additional $MgCl_2$, 1x VENT polymerase buffer (New England Biolabs), and 1 μl VENT polymerase, at 2 units/μl (New England Biolabs). The reaction was denatured at 98° C for 5' then cycled 20 times through the following temperatures: 98° C 1", 98° C 10", 60° C 1", 60° C 1', 72° C 1", 72° C 1' . The reaction was extended for 20' at 72°C before being held at 4° C overnight. This reaction produces a 1579bp fragment which was purified using Qiaquick-spin PCR purification kit (Qiagen) and digested with restriction enzymes ClaI and DraIII (New England Biolabs). The resulting 1515bp fragment was gel purified on a 5% acrylamide gel in 1x TBE, electroeluted in 0.1x TBE, and purified on SpinBind columns (FMC). This insert fragment contains the first 5 immunoglobulin domains of ICAM-1 and the Genenase cleavage site.

The second plasmid, trkcfcgen, is a plasmid for the expression of the TrkC immunoadhesin containing the same portease cleavage site. This plasmid was digested with ClaI (New England Biolabs) completely. This material was then digested with DraIII (New England Biolabs) using sub optimal amounts of the enzyme such that a series of partially cut fragments was generated. The desired 5378bp fragment was isolated on a 0.6% GTG Agarose (FMC) gel run in 1x TBE (BRL) and electroeluted in 0.1X TBE. The material was extracted first with butanol, then phenol, then chloroform and precipitated with 0.1 volume 3M NaAcetate, pH 7.0 and 2.5 volumes of EtOH. This vector fragment contains all of the plasmid features listed above except the first 5 immunoglobulin domains of ICAM-1 and the protease cleavage site.

The two fragments described above were combined in an insert:vector ratio of 3:1 using approximately 50 ng of vector in 1x ligase buffer and 2 μl ligase at 400 units/μl (New England Biolabs) for 2 hrs. at room temperature. Half of the reaction was transformed into MM294 competent cells by standard methods.

Generation of ICAM-1-immunoadhesin expressing 293 cell line

A cell line expressing the ICAM-1-immunoadhesin was generated by transfecting 293 cells with a cDNA encoding the five immunoglobulin domains of human ICAM-1 upstream from the human Fc sequence (pRK.5dICAMGalg,) together with pRSVneo, as previously described for the LFA-1 cell line. Upon selection in 0.8mg/ml G418 individual clones of drug resistant cells were isolated. Culture supernatants from these clones were assayed for expression of the human ICAM-1-immunoadhesin by ELISA, using polyclonal antibodies directed against the human Fc (Caltag catalogue # H10507, H10700.) A clonal cell line expressing approximately 1mg/ml of ICAM-1-immunoadhesin, as measured by Fc ELISA, was found to react with a monoclonal antibody (AMAC clone 84H10, catalogue # 0544) directed against human ICAM-1. This cell line was grown under

serum free culture conditions and culture supernatant was harvested for purification of the ICAM-1-immunoadhesin.

Example 3

ICAM-1:LFA-1 Receptor Binding Assay

(protein/protein assay)

A cartoon illustrating the forward format of the human ICAM-1:LFA-1 Receptor Binding Assay (PPFF) is provided in Figure 2. Competitive inhibition of the CD11a/CD18-ICAM-1 interaction is quantitated by adding known amounts of inhibitors according to the two protein/protein assay systems described below.

Forward Format LFA-1:ICAM-1 Assay (PPFF):

Purified full-length recombinant human LFA-1 protein is diluted to 2.5μg/ml in 0.02M Hepes, 0.15M NaCl, and 1mM $MnCl_2$ and 96-well plates (50μl/well) are coated overnight at 4°C. The plates are washed with wash buffer (0.05% Tween 20 in PBS) and blocked for 1h at room temperature with 1% BSA in 0.02M Hepes, 0.15M NaCl, and 1mM $MnCl_2$. Plates are washed. 50μl/well inhibitors, appropriately diluted in assay buffer (0.5% BSA in 0.02M Hepes, 0.15M NaCl, and 1mM MnCl2), are added to a 2X final concentration and incubated for 1h at room temperature. 50μl/well of purified recombinant human 5 domain ICAM-Ig, diluted to 50ng/ml in assay buffer, is added and incubated 2h at room temperature. Plates are washed and bound ICAM-Ig is detected with Goat anti-HuIgG(Fc)-HRP for 1h at room temperature. Plates are washed and developed with 100μl/well TMB substrate for 10-30' at room temperature. Colorimetric development is stopped with 100μl/well 1M H_3PO_4 and read at 450nM on a platereader.

An alternative protein/protein assay system described below also quantitates competitive inhibition of the CD11a/CD18-ICAM-1 interaction.

PLM2 Antibody Capture LFA-1:ICAM-1 Assay (PLM2):

A non-function blocking monoclonal antibody against human CD18, PLM-2 (as described by Hildreth, *et al., Molecular Immunology*, Vol. 26, No. 9, pp. 883-895, 1989), is diluted to 5μg/ml in PBS and 96-well flat-bottomed plates are coated with 100μl/well overnight at 4°C. The plates are blocked with 0.5% BSA in assay buffer (0.02M Hepes, 0.15M NaCl, and 1mM $MnCl_2$) 1h at room temperature. Plates are washed with 50mM Tris pH 7.5, 0.1M NaCl, 0.05% Tween 20 and 1mM MnCl2. Purified full-length recombinant human LFA-1 protein is diluted to 2μg/ml in assay buffer and 100μl/well is added to plates and incubated 1h at 37°C. Plates are washed 3X. 50μl/well inhibitors, appropriately diluted in assay buffer, are added to a 2X final concentration and incubated for 30' at 37°C. 50μl/well of purified recombinant human 5 domain ICAM-Ig, diluted to 161ng/ml (for a final concentration of 80ng/ml) in assay buffer, is added and incubated 2h at 37°C. Plates are washed and bound ICAM-Ig is detected with Goat anti-HuIgG(Fc)-HRP for 1h at room temperature. Plates are washed and developed with 100μl/well TMB substrate for 5-10' at room

temperature. Colorimetric development is stopped with 100µl/well 1M H_3PO_4 and read at 450nM on a platereader.

Example 4

Human T-cell Adhesion Assay

(cell attachment assay)

A cartoon illustrating the human T cell adhesion colorimetric assay is provided in Figure 3. The T-cell adhesion assay is performed using a human T-lymphoid cell line HuT 78. Goat anti-HuIgG(Fc) was diluted to 2µg/ml in PBS and 96-well plates were coated with 50µl/well @ 37°C for 1h. Plates were washed with PBS and blocked for 1h @ room temperature with 1% BSA in PBS. 5 domain ICAM-Ig was diluted to 100ng/ml in PBS and 50µl/well was added to the plates O/N @ 4°C. HuT 78 cells were centrifuged at 100 g and the cell pellet was treated with 5mM EDTA for ~5' at 37°C in a 5% CO2 incubator. Cells were washed in 0.14M NaCl, 0.02M Hepes, 0.2% Glucose and 0.1mM MnCl2 (assay buffer) and centrifuged. The cells were resuspended in assay buffer to 3.0 x 10^6c/ml. Inhibitors were diluted in assay buffer to a 2X final concentration and pre-incubated with HuT 78 cells for 30' at room temperature. 100µl/well of cells and inhibitors were added to the plates and incubated at room temperature for 1h. 100µl/well PBS was added and the plates were sealed and centrifuged inverted at 100 g for 5'. Unattached cells were flicked out of the plate and excess PBS was blotted on a paper towel. 60µl/well *p*-nitrophenyl *n*-acetyl-β-D-glucosaminide (0.257g to 100ml citrate buffer) was added to the plate and incubated for 1.5h at 37°C. The enzyme reaction was stopped with 90µl/well 50mM Glycine/5mM EDTA and read on a platereader at 405nM. HUT 78 cell adhesion to 5dICAM-Ig is measured using the *p*-nitrophenyl *n*-acetyl-ß-D-glucosaminide method of Landegren, U. (1984)

J. Immunol. Methods 57, 379-388

Example 5

T-Cell Proliferation assay (co-stimulation assay)

A cartoon illustrating the human T cell proliferation assay is provided in Figure 4. This assay is an in vitro model of lymphocyte proliferation resulting from activation, induced by engagement of the T-cell receptor and LFA-1, upon interaction with antigen presenting cells (Springer, *Nature* 346:425 (1990)).

Microtiter plates (Nunc 96 well ELISA certified) were precoated overnight at 4°C with 50µl of 2µg/ml of goat anti-human Fc (Caltag H10700) and 50µl of 0.07µg/ml monoclonal antibody to CD3 (Immunotech 0178) in sterile PBS. The next day coat solutions were aspirated. Plates were then washed twice with PBS and 100µl of 17 ng/ml 5d-ICAM-1-IgG were added for 4 hours at 37°C. Plates were washed twice with PBS prior to addition of CD4+ T cells. Lymphocytes from peripheral blood were separated from heparinized whole blood drawn from healthy donors. An alternative method was to obtain whole blood from healthy donors through leukophoresis. Blood was diluted 1:1 with saline, layered, and centrifuged at 2500 x g for 30 minutes on LSM (6.2g Ficoll and 9.4g

sodium diztrizoate per 100ml) (Organon Technica, NJ). Monocytes were depleted using a myeloid cell depletion reagent method (Myeloclear, Cedarlane Labs, Hornby, Ontario, Canada). PBLs were resuspended in 90% heat-inactivated Fetal Bovine serum and 10% DMSO, aliquoted, and stored in liquid nitrogen. After thawing, cells were resuspended in RPMI 1640 medium (Gibco, Grand island, NY) supplemented with 10% heat-inactivated Fetal Bovine serum (Intergen, Purchase, NY), 1mM sodium pyruvate, 3mM L-glutamine, 1mM nonessential amino acids, 500µg/ml penicillin, 50µg/ml streptomycin, 50µg/ml gentamycin (Gibco).

Purification of CD4+ T cells were obtained by a negative selection method (Human CD4 Cell Recovery Column Kit #CL110-5 Accurate). 100,000 purified CD4+ T cells (90% purity) per microtiter plate well were cultured for 72 hours at 37°C in 5% CO_2 in 100µl of culture medium (RPMI 1640 (Gibco) supplemented with 10% heat inactivated FBS (Intergen), 0.1mM non-essential amino acids, 1nM Sodium Pyruvate, 100 units/ml Penicillin, 100 µg/ml Streptomycin, 50µg/ml Gentamicin, 10mM Hepes and 2mM Glutamine). Inhibitors were added to the plate at the initiation of culture. Proliferative responses in these cultures were measured by addition of 1µCi/well tritiated thymidine during the last 6 hours before harvesting of cells. Incorporation of radioactive label was measured by liquid scintillation counting (Packard 96 well harvester and counter). Results are expressed in counts per minute (cpm).

Example 6

***In vitro* Mixed Lymphocyte Culture Model**

A cartoon depicting the mixed lymphocyte response assay is provided in Figure 5. This mixed lymphocyte culture model, which is an *in vitro* model of transplantation (A.J. Cunningham, "Understanding Immunology, *Transplantation Immunology* pages 157-159 (1978), examines the effects of various LFA-1 antagonists in both the proliferative and effector arms of the human mixed lymphocyte response.

Isolation of Cells: Mononuclear cells from peripheral blood (PBMC) were separated from heparinized whole blood drawn from healthy donors. Blood was diluted 1:1 with saline, layered, and centrifuged at 2500 x g for 30 minutes on LSM (6.2g Ficoll and 9.4g sodium diztrizoate per 100ml) (Organon Technica, NJ). An alternative method was to obtain whole blood from healthy donors through leukophoresis. PBMCs were separated as above, resuspended in 90% heat-inactivated Fetal Bovine serum and 10% DMSO, aliquoted, and stored in liquid nitrogen. After thawing, cells were resuspended in RPMI 1640 medium (Gibco, Grand Island, NY) supplemented with 10% heat-inactivated Fetal Bovine serum (Intergen, Purchase, NY), 1mM sodium pyruvate, 3mM L-glutamine, 1mM nonessential amino acids, 500µg/ml penicillin, 50µg/ml streptomycin, 50µg/ml gentamycin (Gibco).

Mixed Lymphocyte Response (MLR): One way human mixed lymphocyte cultures were established in 96-well flat-bottomed microtiter plates. Briefly, 1.5×10^5 responder PBMCs were co-cultured with an equal number of allogeneic irradiated (3000 rads for 3 minutes, 52 seconds)

stimulator PBMCs in 200µl of complete medium. LFA-1 antagonists were added at the initiation of cultures. Cultures were incubated at 37°C in 5% CO_2 for 6 days, then pulsed with 1µCi/well of ^{3}H-thymidine (6.7 Ci/mmol, NEN, Boston, MA) for 6 hours. Cultures were harvested on a Packard cell harvester (Packard, Canberra, Canada). [^{3}H] TdR incorporation was measured by liquid scintillation counting. Results are expressed as counts per minute (cpm).

Example 7

Compound Synthesis and Activity

Abbreviations used in the following section: Wang resin = p- alkoxybenzyl alcohol resin; Fmoc = 9- fluorenylmethyloxycarbonyl; Fmoc-OSu = 9- fluorenylmethyloxycarbonyl- N-hydroxysuccinimide; Boc = t- butyloxycarbonyl; Boc_2O = *t*- butyloxycarbonyl anhydride; DMA = dimethylacetimide; DMF = dimethylformamide; BOP = (benzotriazol-1-yloxy) tris (dimethyl-amino) phosphonium hexafluorophosphate; Hobt = 1-hydroxybenztriazole; NMM = 4-methylmorpholine; TFA = trifluoroacetic acid; DCM = dichloromethane; MeOH = methanol; HOAc = acetic acid; HCl = hydrochloric acid; H_2SO_4 = sulfuric acid; K_2CO_3 = potassium carbonate; Ph_3P = triphenylphosphine; THF = tetrahydrofuran; EtOAc = ethyl acetate; DIPEA = diisopropylethylamine; $NaHCO_3$ = sodium bicarbinate; NMP = N-methyl pyrrolidinone; DIPC = diisopropylcarbodiimide; ACN = acetonitrile; HBTU = 2-(1H-benzotriazole-1-yl)-1, 1, 3, 3-tetramethyluronium hexafluorophosphate; NCS = N-chlorosuccinimide; Na_2•EDTA = ethylenediaminetetraacetic acid sodium salt; TBAF = tetrabutyl ammonium fluoride; EDC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide•HCl; DEAD = diethyl azocarboxylate; TEA = triethylamine; $MgSO_4$ = magnesium sulfate; TES = triethylsilane; Et_2O = diethyl ether; BBr_3 = boron tribromide

General synthetic methods

Method G1

The appropriate Boc protected molecule was dissolved in a solution of TFA in DCM (1:1). After 20 minutes, the reaction was concentrated *in vacuo*. The resulting oil was dissolved in toluene and then concentrated *in vacuo* twice.

Method G2

The appropriate amine was dissolved in Et_2O and washed twice with a 10% solution of K_2CO_3 in H_2O and once with brine. The organic layer was then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was then used with out further purification.

Method G3

3 equivalents of the appropriate carboxylic acid was coupled to 1 equivalent of the appropriate amine using 3 equivalents EDC and 1 equivalent of Hobt in DMA. The reaction was monitored by TLC (9/1 DCM/MeOH). Upon completion, the mixture was concentrated *in vacuo*. The resulting oil was re suspended in Et_2O and washed twice with 0.1 N H_2SO_4, twice with saturated $NaHCO_3$, and once with brine. The organic layer was then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was then used with out further purification.

Method G4

1 equivalent of the appropriate methyl ester was dissolved in THF/H_2O (3/1) and 3 equivalents of $LiOH \cdot H_2O$ was added. The reaction was monitored by TLC (9/1 DCM/MeOH). Upon completion, the mixture was acidified carefully to pH 2 with concentrated HCl and then concentrated *in vacuo*. The resulting solid was re suspended in Et_2O and washed twice with 0.1 N H_2SO_4 and once with brine. The organic layer was then dried over $MgSO_4$, filtered and concentrated *in vacuo*.

Method G5

1 equivalent of the appropriate amino acid and 2.5 equivalents of $NaHCO_3$ were dissolved in THF/H_2O (3/1). Once the solution becomes clear, 1.5 equivalents of Fmoc-OSu was added. The reaction was monitored by TLC (9/1 DCM/MeOH). Upon completion, the mixture was concentrated *in vacuo* until only the aqueous phase remained. The aqueous solution was then extracted twice with Et_2O and then acidified carefully to pH 2 with concentrated HCl to precipitate out the product. The aqueous layer and product was then extracted with EtOAc. The organic layer was then partitioned once with brine and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting product was used without further purification.

Method G6

1 equivalent of fluorenylmethanol and 2.5 equivalents of Hobt was dissolved in NMP. The mixture was cooled to 0°C with stirring. Once cool, 1 equivalent of DIPC was added over 5 minutes with stirring followed by portion wise additions of 1 equivalent of 2- bromoterephthalic acid and then 0.01 equivalents of 4- pyrrolidinopyridine. The mixture was stirred at 0°C for 2 hours, warmed to room temperature and stirred for 4 hours, and then recooled to 0°C and quenched with the drop wise addition of H_2O. After stirring for 1 hour, the mixture was partitioned with EtOAc. The organic layer was then partitioned twice with dilute HCl, once with brine and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product (a 9:1 mixture of correct versus incorrect isomer) was purified using flash silica chromatography using 3/1 hexanes/EtOAc and 3% HOAc.

Method G7

The appropriate methoxy containing compound was dissolved in DCM and cooled to -5°C in an ice/acetone bath under nitrogen. 2 equivalents of BBr_3 was added drop wise as a solution in DCM over 30 minutes. The reaction was warmed to room temperature and stirred until complete by TLC (DCM/2% HOAc/2% MeOH). The solution was poured onto ice, and the ice was allowed to melt. The mixture was then partitioned twice with EtOAc and the combined organic layers were dried over $MgSO_4$. The filtrate was then passed over a plug of silica gel and concentrated *in vacuo*.

Method G8

1 equivalent of dimethyl 2- chloroterephthalic acid was mono hydrolyzed by Method G9 to afford the correct mono protected diacid. The mono ester was then *t*- butyl esterified by Method G10. The methyl ester was then removed by Method G4 to yield the carboxylic acid (Compound A).

Method G9

The diester was dissolved in DCM and cooled to -5°C in an ice/acetone bath under nitrogen. 1 equivalent of BBr_3 was added drop wise as a solution in DCM over 30 minutes. The reaction was warmed to room temperature and stirred until complete by TLC (DCM/2% HOAc/2% MeOH). The solution was poured onto ice, and the ice was allowed to melt. The mixture was then partitioned with EtOAc and concentrated *in vacuo*. This product was dissolved in H_2O with the addition of saturated $NaHCO_3$ until the pH remained above 8. This solution was partitioned one time with and equal volume of DCM to remove unreacted diester. The basic solution was acidified at O°C. with concentrated HCl to pH = 1-1.5, and precipitate was extracted twice with equal volumes of EtOAc. The oraganics were partitioned once with brine and dried over $MgSO_4$, filtered and concentrated *in vacuo*. Product was 7:1 of the correct regioisomer by HPLC.

Method G10

The monoester was dissolved in DCM was transferred to pre-weighed Parr flask containing a stirring bar. The flask was cooled to -5°C with a dry ice/alcohol bath under nitrogen. Once cool, ~30 equivalents of isobutylene was pumped into solution with stirring. 2.1 equivalents of concentrated sulfuric acid was added and the flask was sealed with a wired rubber stopper and allowed to warm to room temperature with stirring. The solution was stirred until clarification (1-2 days). Once the solution was clear, it was cooled to 0°C in an ice bath. The stopper was removed and the excess isobutylene was blown off with nitrogen bubbling. Saturated $NaHCO_3$ was added to neutralize the acid and the mixture was concentrated *in vacuo* until no DCM remained. The solution was then partitioned into EtOAc. The oraganics were partitioned twice with dilute HCl, twice with saturated $NaHCO_3$, once with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting product was used with no further purification.

Method G11

The *t*- butyl ester product was dissolved in DCM and an equal volume of TFA was added. After 30 minutes the reaction was concentrated *in vacuo* and twice redissolved and concentrated from toluene. The product was used without further purification.

Method G12

Compound A was coupled to 3- chloro benzylamine by Method G3. The *t*- butyl ester was removed by Method G11 to yield the carboxylic acid (Compound B).

Method G13

Compound A was coupled to 3- methoxy benzylamine, Method G38, by Method G3. This product was converted to the methyl ester by Method G15. The methoxy group was demethylated to the phenol by Method G7. The methyl ester was saponified to the carboxylic acid by Method G4 and the final product (Compound C) was used without further purification.

Method G14

1 equivalent of 4- bromo 2- chloro benzoic acid was converted to the methyl ester by Method G15 and the bromine was converted to the nitrile by Method G16. After saponification by

Method G4, the nitrile was reduced to the amine and Fmoc protected by Method G17. The final product (Compound D) was purified by flash silica chromatography (95/5 DCM/MeOH) and verified by electrospray mass spectrometry.

Method G15

The appropriate carboxylic acid was dissolved in dry MeOH and 10 equivalents of HCl/dioxane was added and the mixture was stirred overnight to yield the methyl ester product. The solution was concentrated *in vacuo* and twice redissolved and concentrated from toluene. The final product was purified by flash silica chromatography (95/5 DCM/MeOH) and verified by electrospray mass spectrometry.

Method G16

0.6 equivalents of Zinc cyanide and 0.04 equivalents of tetrakis(triphenylphosphine) palladium(0) were placed in a round bottom flask an purged for 30 minutes with circulating nitrogen. The methyl ester was dissolved in anhydrous DMF and degassed for 30 minutes with nitrogen. Upon completion of degassing, the methyl ester solution was added to the zinc cyanide and palladium via cannula and stirred over night at 80°C. Upon completion of the reaction, the solution was concentrated *in vacuo* and redissolved in EtOAc. The oraganics were partitioned twice with dilute HCl, twice with saturated $NaHCO_3$, once with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was purified by flash silica chromatography (DCM) and verified by electrospray mass spectrometry.

Method G17

1 equivalent of the nitrile was dissolved in THF and cooled to 0°C in an ice bath. Once cool, 4 equivalents of super hydride was added quickly via cannula to the nitrile. After 5 minutes, the reaction was poured onto ice containing 5 equivalents of sulfuric acid and stirred until all of the ice melts. Two volumes of THF was added to the solution and the pH was carefully adjusted to 8 with portion wise additions of $NaHCO_3$. 1.5 equivalents of Fmoc-OSu was added. The reaction was monitored by TLC (9/1 DCM/MeOH). Upon reaction completion, the mixture was concentrated *in vacuo* until only the aqueous phase remained. The aqueous solution was then extracted twice with Et_2O and then acidified carefully to pH 2 with concentrated HCl to precipitate out the product. The aqueous layer and product was then extracted with EtOAc. The organic layer was then partitioned once with brine and dried over $MgSO_4$, filtered and concentrated *in vacuo*.

Method G18

1 equivalent of the appropriate hydroxy carboxylic acid, 2.2 equivalents of *t*-butyldimethyl silyl chloride and 3 equivalents of imidizole were dissolved in DMF and stirred at room temperature. The reaction was monitored by TLC (9/1 DCM/MeOH). Upon reaction completion, the mixture was concentrated *in vacuo*. The resulting oil was re suspended in Et_2O and washed twice with saturated $NaHCO_3$, and once with brine. The organic layer was then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was then used with out further purification.

Method G19

To resin that has been rinsed twice with DMA, a solution consisting of 20% piperidine in DMA was added. After 20 minutes, the resin was filtered and rinsed 5 times with DMA.

Method G20

3 equivalents of the appropriate carboxylic acid was coupled with 3 equivalents of BOP, 1 equivalent of HOBt, , and 6 equivalents of NMM in DMA for 30 minutes. The coupling was monitored by the Kaiser ninhydrin test. If the Kaiser test was positive, the appropriate carboxylic acid was coupled again in the same manner.

Method G21

The molecule was cleaved from the rinsed and dried resin in a solution consisting of 5% triisopropylsilane in TFA for 1 hour. The crude molecule was then concentrated *in vacuo*, purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method G22

3 equivalents of the appropriate amine was coupled with 3 equivalents of BOP, 1 equivalent of HOBt, , and 6 equivalents of NMM in DMA for 60 minutes.

Method G23

The resin was washed successively with DMA, DCM, 20% HOAc in DCM, MeOH and DMF. 2 equivalents of the appropriate aldehyde was dissolved in a minimal volume of 1% HOAc in DMF and added to the freshly rinsed resin. After 5 minutes, 2 equivalents of sodium cyanoborohydride in DMF was added, and the resin was bubbled overnight. The resin was then washed with DMF, 20% DIPEA in DCM, DCM and MeOH. The coupling was monitored by the Kaiser ninhydrin test. If the Kaiser test was positive, the appropriate aldehyde was coupled again in the same manner.

Method G24

3 equivalents of the appropriate carboxylic acid (R) was coupled with 3 equivalents of HBTU, and 3 equivalents of DIPEA, in DMA. The reaction was followed by TLC. Upon completion, the mixture was diluted with EtOAc. The organic layer was partitioned with dilute sulfuric acid, saturated $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting methyl ester product was then used with out further purification.

Method G25

The methyl ester of the appropriate carboxylic acid was made by Method G15 and the phenol was converted to the *t*- butyl ester by Method G10. 1 equivalent of the resulting product was dissolved in a 1:2 mixture of THF and EtOH, and 3 equivalents of lithium chloride and 3 equivalents of sodium borohydride was added and the reaction was stirred overnight. The reaction was quenched with H_2O and concentrated *in vacuo*. The residue was partitioned between EtOAc and H_2O, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude alcohol was purified using silica gel flash chromatography (9:1 hexane/Et_2O).

Method G26

A solution of 1 equivalent of the alcohol and 1.1 equivalents of Ph_3P in THF was cooled to -10°C in an ice-ethanol bath. While stirring, a solution of 1.1 equivalents of the phenol and 1.1 equivalents of DEAD in THF was added drop wise. The cold bath was removed and the reaction was stirred at room temperature overnight. The reaction was concentrated *in vacuo* and the resulting residue was taken up in a minimal amount of DCM and filtered through a plug of silica gel, using DCM as eluent. After concentrating this solution *in vacuo*, the residue was purified using silica gel flash chromatography (8/2/0.5 hexane/DCM/Et_2O) to provide the pure ether.

Method G27

1 equivalent of the alcohol was dissolved in acetone and cooled to -10°C. 1.1 equivalents of Jones reagent was added and the reaction was stirred at room temperature for 2 hours. The reaction was filtered through a plug of silica gel and concentrated *in vacuo*. The residue was partitioned between EtOAc and H_2O. The residue was partitioned between EtOAc and H_2O, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The yellow solid was triturated with Et_2O to remove impurities, providing pure ketone.

Method G28

1 equivalent of the appropriate dihydroxynaphthalene was dissolved in pyridine. 4 equivalents of solid sodium hydride was added followed by 2 equivalents of the bromide and 0.4 equivalents of cuprous chloride. The resulting mixture was stirred vigorously and heated in an oil bath at 100°C for two days. After concentrating *in vacuo*., the residue was partitioned between EtOAc and 1M HCl. The aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was triturated with Et_2O. After filtering the mixture and concentrating the filtrate, the resulting residue was purified using silica gel flash chromatography (5:4:1 hexane/DCM/Et_2O).

Method G29

To a stirred -78°C solution of 1 equivalent of the appropriate methyl ester in dry toluene was added a solution of 1.5 M DIBAL in toluene (1.7 equivalents) drop wise. The reaction mixture was stirred for an additional 2 hours at -78°C or until TLC showed clean formation of product, with only a trace of starting material. The reaction was quenched by slowly adding cold (-78°C) MeOH. The resulting white emulsion was slowly poured into ice-cold 1 N HCl and EtOAc and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified using silica gel flash chromatography (9:1 hexane/Et_2O) to provide the pure aldehyde.

Method G30

1 equivalent of the amido alcohol made by Method G28 and 1.5 equivalents of Ph_3P were dissolved in THF and cooled to -5°C. 1.5 equivalents of DEAD was added drop wise and the reaction was stirred at room temperature overnight. After concentrating the reaction *in vacuo*, the

residue was taken up in a minimal amount of DCM and purified by flash chromatography (9:1 hexane/Et_2O) to provide pure oxazoline.

Method G31

To a stirred -78°C solution of 1 equivalent of the bromide in THF was added 1.6 M n-BuLi (1.05 equivalents) drop wise. After 0.5 hour, 1.1 equivalents of the aldehyde in THF was added via cannula at -78°C and the reaction was stirred at -78°C. After 2 hours, the reaction was quenched with 2 equivalents cold (-78°C) HOAc in THF. The mixture was warmed to room temperature, concentrated *in vacuo*, and the oily residue partitioned between Et_2O and H_2O. The aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified using silica gel flash chromatography (7:3 hexane/Et_2O).

Method G32

The oxazoline alcohol was dissolved in a 13:1 mixture of ethanol and sulfuric acid, then heated at reflux for 3 days. The reaction was concentrated *in vacuo*, and the residue was partitioned between Et_2O and H_2O. The aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified using silica gel flash chromatography(1:1 hexane/Et_2O) to give the pure ethyl ester.

Method G33

To freshly rinsed resin was added, 2.2 equivalents of DIPEA and 2.2 equivalents of the appropriate isocyanate (R) in 1, 2- dichloroethane were added and the resin agitated overnight. The resin was then washed with 10% piperidine in NMP, THF, 30% HOAc in DCM and MeOH.

Method G34

1 equivalent of 4- benzyloxy benzyl alcohol resin (Wang resin) was washed with DMA and DCM. To the resin was added 3 equivalents of the appropriate Fmoc protected amino acid, 3 equivalents of DIPC and 0.5 equivalents of DMAP in DCM. The resin was agitated for 2 hours, rinsed with DCM and DMA. The resin was then treated with 10% acetic anhydride in DCM for 5 minutes. The resin was washed with DCM and MeOH and then dried *in vacuo*.

Method G35

The resin was washed with DCM and chloroform. A fresh 0.14M solution of tetrakis (triphenylphosphine) palladium(0) in 2.5% NMM, 5% HOAc in chloroform was added to the resin. After agitating for 1 hour, the resin was checked by the Kaiser ninhydrin test. If the Kaiser test was negative, a new solution of Pd(0) was made and the reaction done again until a positive Kaiser test results. The resin was rinsed with DCM, MeOH and DCM.

Method G36

The deprotected resin was treated for 1 hour with a solution of 10 equivalents of benzophenone imine and 1.3 equivalents of HOAc in DMA to form the glycine benzophenone imine. After rinsing with DMA the resin was treated with 3.5 equivalents of 2-*t*-butylimino-2-diethylamino-1, 3- dimethylperhydro- 1, 2, 3- diazaphosphorine for 1 hour. 3 equivalents of the

appropriate alkylating agent was added and the reaction agitated for 2 hours. The resin was drained and washed with NMP, 20% DIPEA in DCM, DCM, 10% HOAc in DCM and DCM. The benzophenone was removed with a solution of 10 equivalents of hydroxylamine•HCl in THF/H_2O for 3 hours. The resin was the rinsed with H_2O, THF 20% DIPEA in DCM and DCM.

Method G37

10 equivalents of 2-bromoterephthalic acid, 20 equivalents of HBTU, 20 equivalents of Hobt and 22 equivalents of DIPEA were dissolved in DMA and stirred for 15 minutes yielding the bisactivated 2-bromoterephthalic acid ester. To this solution was added 15 equivalents of 3- hydroxy benzylamine, Method G38, and 15 equivalents of DIPEA yielding the active ester of Compound E. The reaction was stirred for 30 minutes and then it was added to the resin which was then agitated over night.

Method G38

1 equivalent of 3-cyanophenol was placed in a Parr bottle with EtOH, 0.02 equivalents of HCl and 10% (w/w) of 10% Pd on carbon. The vessel was placed in the Parr shaker, charged with 50 psi H2, and shaken for 12 hours. The reaction filtered through a pad of celite and diluted 1:10 with Et_2O. Upon standing over night, fine white needles form. The product was filtered, washed with Et_2O and dried *in vacuo*. The resulting hydrochloride salt was then used with out further purification.

Method G39

The resin was washed with DCM and chloroform. A fresh 0.14M solution of tetrakis (triphenylphosphine) palladium(0) in 2.5% NMM, 5% HOAc in chloroform was added to the resin. After agitating for 2 hours, the resin was drained and rinsed with DCM and DMA. The resin was then treated with 10% DIPEA in DMA for 10 minutes, followed by several DMA washes and then with a 5% solution of diethyldithiocarbamic acid in DMA for 15 minutes. The resin was then rinsed with DMA, DCM, MeOH and DCM.

Method G40

Resin was suspended in ACN and cooled to 0°C. Once cool, 3 equivalents of Ph_3P and 3 equivalents of NCS was added and the resin was agitated for 5 minutes. 6 equivalents of the appropriate aniline was added to the resin and the resin was agitated as it was warmed to room temperature. After an additional 10 minutes at room temperature, the reaction was quenched with 3 equivalents of HOAc and the resin washed with 10% HOAc in ACN, DCM and MeOH.

Method G41

The resin was preactivated with 3 equivalents of HBTU, 3 equivalents of Hobt and 6 equivalents of DIPEA in DMA for 10 minutes. 2 equivalents of the appropriate amine was added, and the resin agitated for 30 minutes. The procedure was repeated again. The resin was rinsed with DMA and DCM.

Method G42

The resin was rinsed with DMA, DCM and dichloroethane. 1.1 equivalents of the appropriate sulfonyl chloride and 3 equivalents of DIPEA were added in dichloroethane and the resin was agitated for 12 hours. The reaction can be followed by the Kiaser ninhydrin test and the procedure repeated until a negative Kiaser test results. The resin was washed with dichloroethane, and DCM.

Method G43

The resin was rinsed with DMA, DCM and dichloroethane. 1.1 equivalents of the appropriate chloroformate and 3 equivalents of DIPEA were added in dichloroethane and the resin was agitated for 12 hours. The reaction can be followed by the Kiaser ninhydrin test and the procedure repeated until a negative Kiaser test results. The resin was washed with dichloroethane, and DCM.

Method G44

1 equivalent of the appropriate amine was dissolved in a 3:2 THF/H_2O solution. 1.1 equivalents of solid $NaHCO_3$ and 1.1 equivalents of Boc_2O were added and the solution was stirred overnight. The reaction was concentrated, and the residue was partitioned between H_2O and Et_2O. The aqueous layer was extracted with Et_2O and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to a solid. Recrystallization out of Et_2O/hexane provided pure product.

Method G45

1 equivalent of the appropriate phenol was dissolved in DCM containing 2.6 equivalents of 2, 6-lutidine and the mixture was cooled to -78°C. After adding 1.25 equivalents of triflic anhydride the stirring reaction was allowed to warm to room temperature overnight. The reaction was then concentrated, and the residue was partitioned between Et_2O and H_2O. The aqueous layer was extracted with Et_2O and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (9:1 hexane/Et_2O) to provide the pure triflate.

Method G46

To a stirring solution of 1 equivalent of the triflate in a 2/1 mixture of DMF/MeOH was added 0.15 equivalents of 1, 3-bis(diphenylphosphino)-propane and 2.5 equivalents of TEA. Carbon monoxide gas was bubbled through this solution for 15 minutes, then 0.15 equivalents of Pd(OAc)2 was added and the reaction was stirred at 70°C for 5-7 hours under an atmosphere of CO (using a balloon filled with CO). The reaction was then concentrated *in vacuo*, and the residue was partitioned between Et_2O and H_2O. The aqueous layer was extracted twice with Et_2O and the combined organic layers were dried over $MgSO_4$, filtered through a plug of silica gel and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (9:1:0.02 hexane/DCM/Et_2O) to provide the pure methyl ester

Method G47

1 equivalent of the appropriate Boc-aniline was dissolved in methanol and the solution saturated with HCl. The reaction was heated at 50°C for 3h, then concentrated *in vacuo*. The pale yellow solid was heated in 35% H_2SO_4 until complete dissolution occurred. Upon cooling the mixture by the addition of ice H_2O the amine bisulfate precipitated. The reaction flask was cooled in an ice bath and the mixture stirred vigorously while 1.1 equivalent of sodium nitrite in H_2O was added drop wise. The reaction was stirred at 0°C for another 1.5 hours After diluting the reaction with H_2O, the reaction was heated at 80°C for 10 hours. The reaction was cooled to room temperature and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (14:6:1 hexane/DCM/Et_2O) to provide the pure phenol.

Method G48

1 equivalent of the appropriate methyl benzoate was dissolved in DCM and 1.5 equivalents of a 1.0M solution of BBr_3 was added. After stirring the reaction overnight, the reaction was quenched with ice and stirred for an additional 1.5 hours. The reaction was extracted three times with Et_2O and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was taken up in a minimal amount of saturated $NaHCO_3$. The product was precipitated from this aqueous solution by the addition of concentrated HCl and then extracted into Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to provide pure benzoic acid.

Method G49

1 equivalent of the appropriate carboxylic acid was dissolved in DMF. 1.1 equivalents of solid $NaHCO_3$ and 5 equivalents of allyl bromide were added and the resulting mixture was stirred at 45°C overnight. The reaction was then concentrated, and the residue was partitioned between Et_2O and H_2O. The aqueous layer was extracted three times with Et_2O and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* . The residue was purified by silica gel flash chromatography (7:3 hexane/Et_2O) to provide the pure allyl ester.

Method G50

To a solution of 1 equivalent of the appropriate allyl ester in THF was added 0.1 equivalents of tetrakis (triphenylphosphine) palladium(0) and 10 equivalents of morpholine. The reaction was stirred for 1.5 hours, then concentrated *in vacuo*. The residue was taken up in DCM, extracted three times with 1N HCl, dried over $MgSO_4$ and concentrated *in vacuo* . The residue was triturated with 1:1 hexane/Et_2O, filtered through a plug of glass wool and concentrated *in vacuo* to provide the pure benzoic acid.

Method G51

1 equivalent of the phenol was dissolved in DMF and 2.05 equivalents of K_2CO_3 and 4 equivalents of 1, 3-dibromopropane were added. The reaction was stirred overnight while heating the reaction flask in an oil bath maintained at 50°C. After concentrating the mixture *in vacuo.*, the

residue was partitioned between Et_2O and H_2O. The aqueous layer was extracted three times with Et_2O and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (95:5 hexane/Et_2O) to provide the pure bromide.

Method G52

1 equivalent of the appropriate hydroxy phenol and 1 equivalent of K_2CO_3 were added to a solution of 0.5 equivalents of the bromide in DMF. After stirring overnight, the reaction was concentrated *in vacuo*. The residue was partitioned between Et_2O and H_2O. The aqueous layer was extracted three times with Et_2O and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (18:1 DCM/Et_2O) to provide the pure phenol.

Method G53

To a nitrogen purged glass pressure tube was added 1 equivalent of the appropriate bromide, 5 equivalents of n-butyl vinyl ether, 15 equivalents of TEA, 0.1 equivalents of 1, 3-bis(diphenylphosphine)propane, 1 equivalent of thallium acetate, 0.09 equivalents of palladium acetate, and DMF. The tube was capped and heated to 100°C overnight. The reaction was cooled and the catalyst filtered off. The mixture was diluted with EtOAc and washed with H_2O, and dried over $MgSO_4$. The crude product was purified on silica (4/1 hexane/DCM). This was dissolved in THF and 4N HCl in dioxane and stirred overnight. The solvents were evaporated and the product purified on silica (4/1 hexane/EtOAc) to give pure product.

Method G54

1 equivalent of the appropriate Boc-aniline was dissolved in methanol and the solution saturated with HCl. The reaction was heated at 50°C for 3h, then concentrated *in vacuo*. The pale yellow solid was heated in 35% H_2SO_4 until complete dissolution occurred. Upon cooling the mixture by the addition of ice H_2O the amine bisulfate precipitated. The reaction flask was cooled in an ice bath and the mixture stirred vigorously while 1.1 equivalents of sodium nitrite in H_2O was added drop wise. The reaction was stirred at 0°C for another 1.5 hours. An aqueous solution of 10 equivalents of KI was added, followed immediately with 17 equivalents CuI. The reaction was stirred at room temperature for 14 hours, then extracted 3 times with Et_2O. The combined organic layers were washed with 1M $NaHCO_3$, brine, and dried over $MgSO_4$, then concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (95:5 hexane/Et_2O) to provide the pure iodide.

Method G55

2.3 equivalents of lithium iodide was added to 1 equivalent of methyl- 2, 6-dichloro- 4-iodobenzoate in pyridine, and the mixture heated at reflux for 8 hours. The reaction was concentrated *in vacuo* and the residue was partitioned between EtOAc and 1N HCl. The aqueous layer was extracted three times with EtOAc, and the combined organic layers were washed with 1M $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in NMM and the

solution concentrated *in vacuo*. The residue was taken up in DCM and then washed three times with 1N HCl. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to provide the benzoic acid in high enough purity to be used without further purification.

Method G56

1.3 equivalents of DIPEA was added to a heterogeneous mixture of 1 equivalent of 3-hydroxybenzoic acid, 1.3 equivalents of N, O-dimethylhydroxylamine hydrochloride, 1.3 equivalents of HOBt and 1.3 equivalents of EDC stirring in DMF. All solids eventually dissolved as the mixture was stirred at room temperature for 28 hours. After concentrating the mixture, the residue was partitioned between Et_2O and H_2O. The aqueous layer was extracted three times with Et_2O and the combined organic layers were dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (Et_2O) to provide the pure hydroxamate.

Method G57

To a stirred -78°C solution of 1 equivalent of the appropriate protected hydroxamate in THF was added a solution of 1.2 equivalents of 1.5 M DIBAL in toluene drop wise. The reaction mixture was stirred for an additional 3 hours at -78°C or until TLC showed clean formation of product, with only a trace of starting material. The reaction was quenched by adding to a separatory funnel containing Et_2O and 0.35M $NaHSO_4$. The layers were separated. The aqueous layer was extracted three times with ethyl ether. The combined organic layers were washed twice with 1N HCl, saturated aqueous $NaHCO_3$, and over $MgSO_4$, filtered through a plug of silica gel, and concentrated *in vacuo*. No further purification of the aldehyde was necessary.

Method G58

A solution of 1 equivalent of the appropriate aldehyde in THF was cooled to -78°C and 1.1 equivalents of 0.5M ethynylmagnesium bromide/THF was added. After stirring the reaction at room temperature for 3 hours, it was diluted with Et_2O and washed twice with 10% citric acid. The combined aqueous layers were back-extracted once with Et_2O. The combined organic layers were washed twice with saturated aqueous $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (4:1 to 3:2 hexane/Et_2O) to provide the pure alkyne.

Method G59

1 equivalent of the aryl iodide was dissolved in EtOAc and the solution was degassed by passing N2 through a pipette and into the solution for 10 minutes. 1.25 equivalents of the alkyne was added, followed by 0.02 equivalents of dichlorobis(triphenylphosphine)palladium(II), 0.04 equivalents of CuI and 5 equivalents TEA. The reaction was stirred for 14 hours, diluted with EtOAc, washed twice with 5% Na_2•EDTA, brine and then dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (gradient elution, using Et_2O to EtOAc) to provide the pure aryl alkyne.

Method G60

1 equivalent of the aryl alkyne was dissolved in MeOH and the solution was degassed by passing N2 through a pipette and into the solution for 10 minutes. The 5% Rh/Al_2O_3 was added, one balloon-full of hydrogen was passed through the solution, and the reaction was stirred under an atmosphere of H_2 (using a balloon) for 7 hours, after which the reaction was filtered through a pad of celite and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (gradient elution, using Et_2O to EtOAc) to provide the pure product.

Method G61

2 equivalents of the appropriate protected amino acid and 2 equivalents of Ph_3P was suspended in DCM. 2.2 equivalents of NCS was added and the mixture was stirred for 30 minutes. 1 equivalent of the aniline containing resin and 1.1 equivalents of NMM was suspended in DCM and the clear acid solution added. The resin was agitated for 2 hours, rinsed with DCM, DMA and DCM. The procedure was repeated again.

Method G62

The appropriate benzaldehyde was converted to its corresponding hydantoin by Method G63 and then hydrolyzed to the amino acid by Method G64. The pure racemic amino acid was then protected by Method G5.

Method G63

1 equivalent of the appropriate benzaldehyde, 2 equivalents of potassium cyanide and 4 equivalents of ammonium carbonate were refluxed in 50% EtOH for 2.5 hours. After cooling to 0°C, the solution was acidified to pH 2 will concentrated HCl. After standing in the refrigerator overnight, the crystals were filtered and washed with H_2O and recrystalized from boiling H_2O/EtOH.

Method G64

The pure hydantoin was refluxed in 10% NaOH overnight. After cooling, activated carbon was added and the solution filtered through celite. The solution was acidified to pH 7 with concentrated HCl and allowed to stand in the refrigerator overnight. The resulting crystals were filtered, washed with H_2O and dried overnight *in vacuo* to give pure racemic amino acid.

Method G65

4-bromo-2-chlorobenzoic acid was converted to the *t*-butyl ester by Method G10. *t*-Butylvinyl ether was coupled to the bromide by Method G53 to give 4-acetyl-2-chlorobenzoic acid *t*-butyl ester. The ketone was reduced to the alcohol by Method G66 and the racemic mixture resolved by Method G67 to give pure S isomer. Phthalamide was coupled to the alcohol by Method G68 and the product hydrolyzed by Method G69 to give the amine.

Method G66

2 equivalents of the appropriate ketone was dissolved in MeOH and 1 equivalent of $NaBH_4$ was added. After stirring for 1 hour, the reaction was quenched with concentrated HCl and

concentrated *in vacuo*. The residue was partitioned between Et_2O and H_2O. The organics were dried over $MgSO_4$ and concentrated *in vacuo*. The alcohol can be used without further purification.

Method G67

1 equivalent of the alcohol mixture was dissolved in diisopropyl ether and 2 equivalents of vinylacetate and Amano lipase P (100mg) were added. The suspension was stirred overnight and then concentrated *in vacuo*. The residue was purified by silica get flash chromatography (5/1 EtOAc/hexane) to give pure R and S isomers.

Method G68

A solution of 1 equivalent of the alcohol and 3 equivalents of Ph_3P in THF was cooled to -10°C in an ice-EtOH bath. While stirring, a solution of 3 equivalents of the amine and 3 equivalents of DEAD in THF was added drop wise. The cold bath was removed and the reaction was stirred at room temperature overnight. The reaction was concentrated *in vacuo* and the resulting residue was taken up in a minimal amount of DCM and filtered through a plug of silica gel, using DCM as eluent. After concentrating this solution *in vacuo*, the residue was purified using silica gel flash chromatography (8/2/0.5 hexane/DCM/Et_2O) to provide product.

Method G69

1 equivalent of the phthalamide was dissolved in EtOH and THF followed by addition of 8 equivalents of hydrazine hydrate. The reaction was stirred at room temperature for 1.5 hours, then at 50°C for 1 hour. The solution was cooled, filtered and the solids washed with EtOAc. The clear solution was concentrated *in vacuo* and the residue purified by silica gel flash chromatography (94/4 DCM/MeOH) to give pure amine.

Method G70

1 equivalent of the appropriate commercially available ketone, 5 equivalents of hydroxylamine hydrochloride and 10 equivalents of sodium acetate were combined in MeOH and stirred overnight. The reaction was concentrated *in vacuo* and the residue was partitioned between EtOAc and saturated $NaHCO_3$. The organic layer was washed once with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by silica gel flash chromatography (Et_2O) to give pure oxime.

Method G71

1 equivalent of the appropriate benzaldehyde was treated with 2.5 equivalents of the appropriate R'MgBr in THF at -20°C under an N_2 atmosphere. After warming to room temperature, the reaction was poured into a slurry of 0.1 N sulfuric acid and ice, and the product extracted with EtOAc. After partitioning and washing with brine, the organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to give crude product. Oxidation to the ketone was carried out in dioxane with 1.1 equivalents of 2, 3-dichloro-5, 6-dicyano-1, 4-benzoquinone for 48 hours. Reaction contents were filtered, and the filtrate concentrated *in vacuo* . The residue was purified by silica gel flash chromatography (hexane/EtOAc 1:1) to yield the product as a yellow solid.

Method G72

The resin with the S-trityl or O-trityl protecting group was washed three times with DCM. It was then washed three times for 10 minutes with a solution consisting of 1% TFA 1% TES in DCM. It was then washed 3 times with DCM. The resin was then checked by placing a small amount of resin into a test tube and treating it with concentrated TFA. If no yellow color appears the removal was complete. If a yellow color appears, the above procedure was repeated until a clear test was achieved.

Method G73

The resin containing the appropriate free hydroxyl was washed three times with DCM. A solution of 10% DIPEA in DCM was added to the resin and a 0.3 M solution of phosgene in toluene was added to the resin. The reaction was allowed to proceed for 10 minutes at room temperature, after which it was drained and washed three times with DCM. A 0.3 M solution in DCM of the appropriate amine was added to the resin and it was allowed to react overnight. The resin was then drained and washed three times with DCM.

Method G74

The appropriate resin was washed three times with DCM and then treated with a 0.3 M solution of the appropriate chloroformate (R) in 0.33 M DIPEA in NMP overnight. The coupling was monitored by the Kaiser ninhydrin test. If the Kaiser test was positive, the appropriate chloroformate was coupled again in the same manner. The resin was then washed three times with NMP and then three times with DCM.

Method G75

The appropriate 2, 6- disubstituted phenol (2, 6- dichlorophenol for Compound F; 2; 6-dimethylphenol for Compound H and 2, 6- difluorophenol for Compound I) was alkylated by Method G76. The resulting phthalimide was hydrolyzed and protected by Method G77. The phenol was then converted to the triflate by Method G78 and carbonylated by Method G79 to give the desired double protected compound.

Method G76

A round bottom flask was equipped with an efficient overhead stirrer and charged with concentrated H_2SO_4 (2.7 x volume of H_2O) and H_2O and cooled to ~-5°C with an ethanol ice bath. Once cool, 1 equivalent of the appropriate disubstituted phenol and 1 equivalent of N-(hydroxymethyl)phthalimide were added with vigorous stirring. The reaction was kept cool for 4 hours and then allowed to warm to room temperature overnight with constant stirring. The reaction generally proceeds to a point where there was just a solid in the round bottom flask. At this point EtOAc and H_2O were added and stirred into the solid. Large chunks were broken up and then the precipitate was filtered and washed with more EtOAc and H_2O. The product was then used without further purification after drying overnight in a vacuum desiccator.

Method G77

1 equivalent of the product from Method G76 and (22.5ml x #g of starting material) of methanol was added to a round bottom flask equipped with a H_2O condenser and stirring bar. 1.2 equivalents of hydrazine mono hydrate was added and the mixture was refluxed for 4 hours. After cooling to room temperature, (4.5ml x #g of starting material) of concentrated HCl was carefully added. Upon completion of the addition, the mixture was refluxed again overnight (> 8 hours). The reaction was cooled to 0°C and the precipitated by- product filtered off. The filtrate was then concentrated *in vacuo*. The residue was then Boc protected by Method G44 with the exception that the product was recrystalized from hot methanol and H_2O.

Method G78

1 equivalent of the appropriate phenol and 1.5 equivalents of 2, 6- lutidine was dissolved, with mild heating if necessary, in DCM in a round bottom flask. Once the starting material has completely dissolved, the mixture was cooled to -78°C under N_2 with a dry ice ethanol bath. Once cool, 2.5 equivalents of triflic anhydride was added and the reaction was allowed to slowly come to room temperature with stirring. The reaction was monitored by TLC and was generally done in 4 hours. Upon completion, the reaction was concentrated *in vacuo* and the residue partitioned between EtOAc and H_2O. The organic layer was washed twice with 0.1N H_2SO_4, twice with saturated $NaHCO_3$, once with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was then purified on silica gel using DCM as eluent.

Method G79

1 equivalent of triflate was dissolved in DMF and MeOH in the glass insert of a high pressure Parr bomb. The starting material was then degassed while stirring with CO for 10 minutes. 0.15 equivalents palladium(II) acetate and 0.15 equivalents of 1, 3- bis(diphenylphosphino) propane were then added and the mixture was then degassed while stirring with CO for another 10 minutes. 2.5 equivalents of diisopropyl ethyl amine was added and the Parr bomb assembled. After properly assembling the bomb, it was charged with 300 psi CO gas and heated to 70°C with stirring overnight. The bomb was then cooled and vented. The mixture was transferred to a round bottom flask and concentrated *in vacuo*. The residue was then purified on silica gel using DCM with 1% acetone and 1% TEA as eluent.

Method G81

1 equivalent of the appropriate alkene and 1.5 equivalents of KOH were dissolved in H_2O in an appropriately sized Parr shaker flask. A small amount (approximately 100mg per 50 mmol of alkene) of 5% Pd/C catalyst was added and the flask was charged with 50 psi H_2 and shaken overnight. The mixture was then filtered through Celite and concentrated *in vacuo*. The resulting product was used without further purification.

Method G80

1 equivalent of the appropriate ethyl ester and 1.5 equivalents of KOH was dissolved in H_2O and refluxed for three hours. After completion, the reaction was concentrated *in vacuo* and the product used without further purification.

Method G82

1.2 equivalents of NaH (60% mineral oil dispersion) was suspended in benzene and cooled to 0°C with and ice H_2O bath. 1.2 equivalents of triethyl phosphonoacetate was added slowly and the reaction was allowed to stir until the solution becomes clear. 1 equivalent of the appropriate ketone (R) was added slowly and the reaction was stirred for 4 hours. Upon completion, the reaction was partitioned with toluene and H_2O. The aqueous layer was back extracted. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* . The residue was purified by silica gel flash chromatography (85:15 hexane/EtOAc).

Method G83

1.2 equivalents of NaH (60% mineral oil dispersion) was suspended in benzene and cooled to -10°C with and a dry ice H_2O bath. 1.2 equivalents of triethyl 2- phosphonopropionate was added slowly and the reaction was allowed to stir until the solution becomes clear. 1 equivalent of the appropriate aldehyde (R) was added slowly and the reaction was stirred for 4 hours. Upon completion, the reaction was partitioned with toluene and H_2O. The aqueous layer was back extracted. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* . The residue was purified by silica gel flash chromatography (85:15 hexane/EtOAc).

Method G84

1 equivalent of the appropriately protected toluene was dissolved in acetic anhydride and HOAc, then cooled in an ice-salt bath (-5°C) before concentrated H_2SO_4 was added. A solution of CrO_3 (2.6 equivalents) in acetic anhydride and HOAc was added drop wise and the reaction was stirred for 3.5 hours at -5°C. The reaction was poured into ice H_2O and stirred for 30 min. The mixture was extracted three times with ethyl ether. The combined organic layers were washed with saturated $NaHCO_3$ and brine, then dried over $MgSO_4$ and concentrated *in vacuo* to an oil. Toluene was added to the oil and the solution concentrated *in vacuo* again. This was repeated to obtain a crystalline solid. The solid was dissolved in methanol and concentrated HCl and heated at reflux for 12 hours. The reaction was concentrated *in vacuo* and the residue was purified by silica gel flash chromatography (9:1 hexane/Et_2O) to provide the pure aldehyde.

Method G85

1 equivalent of the appropriate alcohol was dissolved in DMF and cooled to -5°C in an ice-salt H_2O bath. 1.4 equivalents lithium bis(trimethylsilyl)amide in THF was added drop wise. The reaction was stirred for 0.5 hour, then 1 equivalent of methyl iodide was added and the reaction was stirred overnight under an atmosphere of nitrogen. The reaction was partitioned between ethyl ether and 10% citric acid. The aqueous layer was extracted with ethyl ether, the combined organic layers were washed with saturated $NaHCO_3$ and brine, then dried over $MgSO_4$ and concentrated *in*

vacuo to an oil. The residue was purified by silica gel flash chromatography (9:1 hexane/Et_2O) to provide the pure methyl ether.

Method G86

Commercially available nitroterephthalic acid was converted to its diethyl ester by Method G87. The nitro group was replaced by a benzyl mercaptan by Method G88 and deprotected by $AlBr_3$ using Method G89. The thiol was then alkylated with bromoacetaldehyde diethyl acetal by Method G90 and then dehydrated by Method G91. The diethyl ester was treated with LiOH, Method G4, and then coupled by Method G3 to 3-hydroxy benzyl amine, Method G38. The final ethyl ester was removed by Method G4.

Method G87

1 equivalent of the appropriate commercially available carboxylic acid was dissolved in toluene with an excess of ethanol and 0.6 equivalents of H_2SO_4 and the mixture refluxed for 4 days. Upon completion, the reaction was concentrated *in vacuo* and partitioned between EtOAc and H_2O. The organic layer was washed with saturated $NaHCO_3$, brine, dried over $MgSO_4$ and concentrated *in vacuo*. The product was used without further purification.

Method G88

1.25 equivalents of 95% NaH was suspended in DMF and cooled under N_2 to -5°C with an ice bath. 1.25 equivalents of benzyl mercaptan was added drop wise and the solution was allowed to stir for 40 minutes. 1 equivalent of the appropriate aryl nitro compound was added over 20 minutes and the mixture was stirred for an additional 30 minutes. After verifying that reaction was complete, the solution was poured onto ice and stirred until all the ice melts. The aqueous solution was partitioned three times with EtOAc and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (1:4 hexane/EtOAc) to provide product.

Method G89

1 equivalent of benzyl protected material and 2.2 equivalents of $AlBr_3$ were refluxed in toluene for 3 hours at which time H_2O and enough EtOAc was added to partition the mixture. The organic layer was washed three times with H_2O, brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (4:1 hexane/EtOAc) to provide product.

Method G90

1 equivalent of the thiol was dissolved in DMF and 2 equivalents of K_2CO_3 was added. 1.1 equivalents of bromoacetaldehyde diethyl acetal was added slowly over 20 minutes and then 0.1 equivalent of NaI was added portion wise. The reaction was stirred for 2 hours and then partitioned between EtOAc and H_2O. The organic layer was washed three times with H_2O, brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (9:1 hexane/EtOAc) to provide product.

Method G91

1 equivalent (by weight) of the appropriate diethyl acetal and 2 equivalents (by weight) of poly phosphoric acid were dissolved in chlorobenzene. The reaction was monitored by TLC. Upon completion of the reaction, the mixture was concentrated *in vacuo* and then partitioned between EtOAc and saturated $NaHCO_3$. The organic layer was washed twice more with saturated $NaHCO_3$, brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (4:1 hexane/EtOAc) to provide product.

Method G92

1 equivalent of the appropriate carboxylic acid was dissolved in DCM and cooled to 0°C with an ice H_2O bath. Once cool, 3 drops of DMF and 1.5 equivalents of oxalyl chloride were added. The reaction was stirred at 0°C for 1.5 hours and then for 0.5 hour at room temperature. At this time, the reaction was concentrated *in vacuo* and used immediately.

Method G93

1 equivalent of bis-N-carboxybenzoyl-cystine dibenzyl ester was dissolved in HOAc/H_2O (9/1) and treated with chlorine gas for 10 minutes. The reaction was concentrated *in vacuo*, dissolved in toluene and concentrated *in vacuo* again to yield a white solid. This product was dissolved in DCM and 0.5 equivalents of the appropriate amine (R) was added. The reaction was stirred for 30 minutes and then diluted with EtOAc and partitioned with 0.1N H_2SO_4 and then brine. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (EtOAc/hexane 1:1) to yield pure product. The protecting groups were removed by Method G38 and the product used without further purification.

Specific Example methods

Method S1

Compounds were synthesized using standard Fmoc solid phase methods on Fmoc- L-diamiopropionic acid (alloc)- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L- Dapa(alloc)-Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-N-β-Alloc-L-diaminopropionic acid. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The Alloc group was removed by Method G35 The appropriate isocyanate (R) was coupled by Method G33. The completed molecule was worked up by Method G21.

Method S2

Compounds were synthesized using standard Fmoc solid phase methods on Fmoc- L-diamiobutyric acid (alloc)- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L- Daba(alloc)- Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-N-γ-Alloc-L-diaminobutyric acid. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The Alloc group was removed by Method G35 The appropriate isocyanate (R) was coupled by Method G33. The completed molecule was worked up by Method G21.

Method S3

Compounds were synthesized using standard Fmoc solid phase methods on Fmoc- L-Ornithine (alloc)- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L- Orn(alloc)- Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-N-δ-Alloc-L-Ornithine. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The Alloc group was removed by Method G35 The appropriate isocyanate (R) was coupled by Method G33. The completed molecule was worked up by Method G21.

Method S4

Compounds were synthesized using standard Fmoc solid phase methods on Fmoc- L-Lysine (alloc)- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L- Lys(alloc)- Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-N-ε-Alloc-L-lysine. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The Alloc group was removed by Method G35 The appropriate isocyanate (R) was coupled by Method G33. The completed molecule was worked up by Method G21.

Method S5

Compounds were synthesized using standard Fmoc solid phase methods on Fmoc- L-diamiopropionic acid (alloc)- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L- Dapa(alloc)- Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-N-β-Alloc-L-diaminopropionic acid. The Fmoc group was cleaved by Method G19. Compound C, Method G13 was coupled by Method G20. The Alloc group was removed by Method G35. The appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S6

Compounds were synthesized using standard Fmoc solid phase methods on Fmoc- L-diamiobutyric acid (alloc)- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L- Daba(alloc)- Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-N-γ-Alloc-L-diaminobutyric acid The Fmoc group was cleaved by Method G19. Compound C, Method G13 was coupled by Method G20. The Alloc group was removed by Method G35. The appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S7

Compounds were synthesized using standard Fmoc solid phase methods on Fmoc- L-Ornithine (alloc)- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L- Orn(alloc)- Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-N-δ-Alloc-L-Ornithine. The Fmoc group was cleaved by Method G19. Compound C, Method G13 was coupled by Method G20. The Alloc group was removed by Method G35. The appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S8

Compounds were synthesized using standard Fmoc solid phase methods on Fmoc- L-Lysine (alloc)- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L- Lys(alloc)- Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-N-ε-Alloc-L-lysine. The Fmoc group was cleaved by Method G19. Compound C, Method G13 was coupled by Method G20. The Alloc group was removed by Method G35. The appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S9

Compounds were synthesized using standard Fmoc solid phase methods on Fmoc- L-diamiopropionic acid (alloc)- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L- Dapa(alloc)-Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-N-β-Alloc-L-diaminopropionic acid. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The Alloc group was removed by Method G35. Commercially available Fmoc- nipecotic acid was coupled by Method G20. The Fmoc group was removed by Method G19 and the appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S10

Compounds were synthesized using standard Fmoc solid phase methods on Fmoc- L-diamiopropionic acid (alloc)- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L- Dapa(alloc)-Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-N-β-Alloc-L-diaminopropionic acid. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The Alloc group was removed by Method G35. Commercially available Fmoc- isonipecotic acid was coupled by Method G20. The Fmoc group was removed by Method G19 and the appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S11

Compounds were synthesized using standard Fmoc solid phase methods on Fmoc- L-diamiopropionic acid (alloc)- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L- Dapa(alloc)-Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-N-β-Alloc-L-diaminopropionic acid. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The Alloc group was removed by Method G35. Commercially available Fmoc- 3-aminomethyl benzoic acid was coupled by Method G20. The Fmoc group was removed by Method G19 and the appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S12

Compounds were synthesized using standard Fmoc solid phase methods on Fmoc- L-diamiopropionic acid (alloc)- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L- Dapa(alloc)-Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-N-β-

Alloc-L-diaminopropionic acid. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The Alloc group was removed by Method G35. Commercially available Fmoc- 4-aminomethyl benzoic acid was coupled by Method G20. The Fmoc group was removed by Method G19 and the appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S13

Compounds were synthesized using standard Fmoc solid phase methods on Fmoc- L-diamiopropionic acid (alloc)- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L- Dapa(alloc)-Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-N-β-Alloc-L-diaminopropionic acid. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The Alloc group was removed by Method G35. Commercially available Fmoc- β alanine was coupled by Method G20. The Fmoc group was removed by Method G19 and the appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S14

Compounds were synthesized using standard Fmoc solid phase methods on Fmoc- L-diamiopropionic acid (alloc)- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L- Dapa(alloc)-Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-N-β-Alloc-L-diaminopropionic acid. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The Alloc group was removed by Method G35. Commercially available Fmoc- glycine was coupled by Method G20. The Fmoc group was removed by Method G19 and the appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S15

Compounds were synthesized using standard Fmoc solid phase methods on commercially available Fmoc- L- Ornithine (alloc)- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L-Orn(alloc)- Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-N-δ-Alloc-L-Ornithine. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The Alloc group was removed by Method G35. Commercially available Fmoc- nipecotic acid was coupled by Method G20. The Fmoc group was removed by Method G19 and the appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S16

Compounds were synthesized using standard Fmoc solid phase methods on commercially available Fmoc- L- Ornithine (alloc)- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L-Orn(alloc)- Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-N-δ-Alloc-L-Ornithine. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The Alloc group was removed by Method G35. Commercially

available Fmoc- isonipecotic acid was coupled by Method G20. The Fmoc group was removed by Method G19 and the appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S17

Compounds were synthesized using standard Fmoc solid phase methods on commercially available Fmoc- L- Ornithine (alloc)- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L-Orn(alloc)- Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-N-δ-Alloc-L-Ornithine. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The Alloc group was removed by Method G35. Commercially available Fmoc- pipecolinic acid was coupled by Method G20. The Fmoc group was removed by Method G19 and the appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S18

Compounds were synthesized using standard Fmoc solid phase methods on commercially available Fmoc- L- Ornithine (alloc)- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L-Orn(alloc)- Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-N-δ-Alloc-L-Ornithine. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The Alloc group was removed by Method G35. Commercially available Fmoc- 3-aminomethyl benzoic acid was coupled by Method G20. The Fmoc group was removed by Method G19 and the appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S19

Compounds were synthesized using standard Fmoc solid phase methods on commercially available Fmoc- L- Ornithine (alloc)- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L-Orn(alloc)- Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-N-δ-Alloc-L-Ornithine. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The Alloc group was removed by Method G35. Commercially available Fmoc- 4-aminomethyl benzoic acid was coupled by Method G20. The Fmoc group was removed by Method G19 and the appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S20

Compounds were synthesized using standard Fmoc solid phase methods on commercially available Fmoc- L- Ornithine (alloc)- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L-Orn(alloc)- Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-N-δ-Alloc-L-Ornithine. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The Alloc group was removed by Method G35. Commercially available Fmoc- β alanine was coupled by Method G20. The Fmoc group was removed by Method

G19 and the appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S21

Compounds were synthesized using standard Fmoc solid phase methods on commercially available Fmoc- L- Ornithine (alloc)- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L-Orn(alloc)- Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-N-δ-Alloc-L-Ornithine. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The Alloc group was removed by Method G35. Commercially available Fmoc- glycine was coupled by Method G20. The Fmoc group was removed by Method G19 and the appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S22

Compounds were synthesized using standard Fmoc solid phase methods on N-α-Fmoc-N-γ-Alloc-L-diaminobutyric acid- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L- Daba(alloc)-Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-N-γ-Alloc-L-diaminobutyric acid. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The Alloc group was removed by Method G35. Commercially available Fmoc- nipecotic acid was coupled by Method G20. The Fmoc group was removed by Method G19 and the appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S23

Compounds were synthesized using standard Fmoc solid phase methods on N-α-Fmoc-N-γ-Alloc-L-diaminobutyric acid- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L- Daba(alloc)-Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-N-γ-Alloc-L-diaminobutyric acid. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The Alloc group was removed by Method G35. Commercially available Fmoc- isonipecotic acid was coupled by Method G20. The Fmoc group was removed by Method G19 and the appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S24

Compounds were synthesized using standard Fmoc solid phase methods on N-α-Fmoc-N-γ-Alloc-L-diaminobutyric acid- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L- Daba(alloc)- Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-N-γ-Alloc-L-diaminobutyric acid. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The Alloc group was removed by Method G35. Commercially available Fmoc- pipecolinic acid was coupled by Method G20. The Fmoc group was removed by Method G19 and the appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S25

Compounds were synthesized using standard Fmoc solid phase methods on N-α-Fmoc-N-γ-Alloc-L-diaminobutyric acid- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L- Daba(alloc)-Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-N-γ-Alloc-L-diaminobutyric acid. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The Alloc group was removed by Method G35. Commercially available Fmoc- 3-aminomethyl benzoic acid was coupled by Method G20. The Fmoc group was removed by Method G19 and the appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S26

Compounds were synthesized using standard Fmoc solid phase methods on N-α-Fmoc-N-γ-Alloc-L-diaminobutyric acid- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L- Daba(alloc)-Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-N-γ-Alloc-L-diaminobutyric acid. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The Alloc group was removed by Method G35. Commercially available Fmoc- 4-aminomethyl benzoic acid was coupled by Method G20. The Fmoc group was removed by Method G19 and the appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S27

Compounds were synthesized using standard Fmoc solid phase methods on N-α-Fmoc-N-γ-Alloc-L-diaminobutyric acid- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L- Daba(alloc)-Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-N-γ-Alloc-L-diaminobutyric acid. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The Alloc group was removed by Method G35. Commercially available Fmoc- β alanine was coupled by Method G20. The Fmoc group was removed by Method G19 and the appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S28

Compounds were synthesized using standard Fmoc solid phase methods on N-α-Fmoc-N-γ-Alloc-L-diaminobutyric acid- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L- Daba(alloc)-Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-N-γ-Alloc-L-diaminobutyric acid. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The Alloc group was removed by Method G35. Commercially available Fmoc- glycine was coupled by Method G20. The Fmoc group was removed by Method G19 and the appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S29

Compounds were synthesized using standard Fmoc solid phase methods on Fmoc- L-Lysine (alloc)- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L- Lys(alloc)- Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-N-ε-Alloc-L-lysine. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The Alloc group was removed by Method G35. Commercially available Fmoc- nipecotic acid was coupled by Method G20. The Fmoc group was removed by Method G19 and the appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S30

Compounds were synthesized using standard Fmoc solid phase methods on Fmoc- L-Lysine (alloc)- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L- Lys(alloc)- Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-N-ε-Alloc-L-lysine. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The Alloc group was removed by Method G35. Commercially available Fmoc- isonipecotic acid was coupled by Method G20. The Fmoc group was removed by Method G19 and the appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S31

Compounds were synthesized using standard Fmoc solid phase methods on Fmoc- L-Lysine (alloc)- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L- Lys(alloc)- Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-N-ε-Alloc-L-lysine. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The Alloc group was removed by Method G35. Commercially available Fmoc- pipecolinic acid was coupled by Method G20. The Fmoc group was removed by Method G19 and the appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S32

Compounds were synthesized using standard Fmoc solid phase methods on Fmoc- L-Lysine (alloc)- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L- Lys(alloc)- Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-N-ε-Alloc-L-lysine. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The Alloc group was removed by Method G35. Commercially available Fmoc- 3-aminomethyl benzoic acid was coupled by Method G20. The Fmoc group was removed by Method G19 and the appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S33

Compounds were synthesized using standard Fmoc solid phase methods on Fmoc- L-Lysine (alloc)- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L- Lys(alloc)- Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-N-ε-Alloc-L-lysine. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The Alloc group was removed by Method G35. Commercially available Fmoc- 4-aminomethyl benzoic acid was coupled by Method G20. The Fmoc group was removed by Method G19 and the appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S34

Compounds were synthesized using standard Fmoc solid phase methods on Fmoc- L-Lysine (alloc)- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L- Lys(alloc)- Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-N-ε-Alloc-L-lysine. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The Alloc group was removed by Method G35. Commercially available Fmoc- β alanine was coupled by Method G20. The Fmoc group was removed by Method G19 and the appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S35

Compounds were synthesized using standard Fmoc solid phase methods on Fmoc- L-Lysine (alloc)- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L- Lys(alloc)- Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-N-ε-Alloc-L-lysine. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The Alloc group was removed by Method G35. Commercially available Fmoc- glycine was coupled by Method G20. The Fmoc group was removed by Method G19 and the appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S36

Compounds were synthesized using standard Fmoc solid phase methods on Fmoc- L-diamiopropionic acid (alloc)- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L- Dapa(alloc)-Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-N-β-Alloc-L-diaminopropionic acid. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The Alloc group was removed by Method G35. The appropriate chloroformate (R) was coupled by Method G74. The completed molecule was worked up by Method G21.

Method S37

Compounds were synthesized using standard Fmoc solid phase methods on commercially available Fmoc- L- tryptophan(Boc)- Wang resin (0.5 mmol/g). The Fmoc group was cleaved by Method G19. Compound D, Method G14, was coupled by Method G20. The Fmoc group was

cleaved by Method G19. The appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S38

Compounds were synthesized using standard Fmoc solid phase methods on commercially available Fmoc- L- alanine- Wang resin (0.5 mmol/g). The Fmoc group was cleaved by Method G19. Compound D, Method G14, was coupled by Method G20. The Fmoc group was cleaved by Method G19. The appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S39

Compounds were synthesized using standard Fmoc solid phase methods on commercially available Fmoc- L- asparagine(Trt)- Wang resin (0.5 mmol/g). The Fmoc group was cleaved by Method G19. Compound D, Method G14, was coupled by Method G20. The Fmoc group was cleaved by Method G19. The appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S40

Compounds were synthesized using standard Fmoc solid phase methods on commercially available Fmoc- L- tryptophan(Boc)- Wang resin (0.5 mmol/g). The Fmoc group was cleaved by Method G19. 4- amino 2- methylbenzoic acid was coupled by Method G20. The appropriate carboxylic acid (R) was silyl protected, Method G18, and the acid chloride generated by Method G92 and coupled in DCM over night to the amine. After washing the resin with DCM and THF, 3 equivalents of tetrabutylammonium fluoride in THF was added. After 20 minutes, the resin was washed with THF, H_2O and dilute HOAc. The completed molecule was worked up by Method G21.

Method S41

Compounds were synthesized using standard Fmoc solid phase methods on commercially available Fmoc- L- amino acid- Wang resins (0.5 mmol/g) (R). The Fmoc group was cleaved by Method G19. 4- amino 2- methylbenzoic acid was coupled by Method G20. The 3- hydroxy phenylacetic acid was silyl protected, Method G18, and the acid chloride generated by Method G92 and coupled in DCM over night to the amine. After washing the resin with DCM and THF, 3 equivalents of TBAF in THF was added. After 20 minutes, the resin was washed with THF, H_2O and dilute HOAc. The completed molecule was worked up by Method G21.

Method S42

Compounds were synthesized using standard Fmoc solid phase methods on commercially available Fmoc- L- alanine- Wang resin (0.5 mmol/g). The Fmoc group was cleaved by Method G19. Commercially available 4- amino 2-chloro benzoic acid was coupled by Method G20. Fmoc- glycine was coupled to the aniline by Method G61. The Fmoc group was cleaved by Method G19. The appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S43

Compounds were synthesized using standard Fmoc solid phase methods on commercially available Fmoc- L- alanine- Wang resin (0.5 mmol/g). The Fmoc group was cleaved by Method G19. Commercially available 4- amino 2-chloro benzoic acid was coupled by Method G20. Fmoc- L-alanine was coupled to the aniline by Method G61. The Fmoc group was cleaved by Method G19. The appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S44

Compounds were synthesized using standard Fmoc solid phase methods on commercially available Fmoc- L- alanine- Wang resin (0.5 mmol/g). The Fmoc group was cleaved by Method G19. Commercially available 4- amino 2-chloro benzoic acid was coupled by Method G20. Fmoc- L-phenylglycine was coupled to the aniline by Method G61. The Fmoc group was cleaved by Method G19. The appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S45

Compounds were synthesized using standard Fmoc solid phase methods on commercially available Fmoc- L- alanine- Wang resin (0.5 mmol/g). The Fmoc group was cleaved by Method G19. Commercially available 4- amino 2-chloro benzoic acid was coupled by Method G20. Fmoc- L-glutamine was coupled to the aniline by Method G61. The Fmoc group was cleaved by Method G19. The appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S46

Compounds were synthesized using standard Fmoc solid phase methods on commercially available Fmoc- L- alanine- Wang resin (0.5 mmol/g). The Fmoc group was cleaved by Method G19. Commercially available 4- amino 2-chloro benzoic acid was coupled by Method G20. 3- chloro benzaldehyde was converted to Fmoc- 3- chloro- phenylglycine by Method G62, and coupled to the aniline by Method G61. The Fmoc group was cleaved by Method G19. The appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S47

Compounds were synthesized using standard Fmoc solid phase methods on commercially available Fmoc- L- diaminopropionic acid(alloc)- Wang resin (0.5 mmol/g). The Fmoc group was cleaved by Method G19. Compound D, Method G14, was coupled by Method G20. The Fmoc group was cleaved by Method G19. The appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S48

Compounds were synthesized using standard Fmoc solid phase methods on commercially available Fmoc- L- Lysine(Boc)- Wang resin (0.5 mmol/g). The Fmoc group was cleaved by Method G19. Compound D, Method G14, was coupled by Method G20. The Fmoc group was cleaved by

Method G19. The appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S49

Compounds were synthesized using standard Fmoc solid phase methods on commercially available Fmoc- L- alanine- Wang resin (0.5 mmol/g). The Fmoc group was cleaved by Method G19. Commercially available 4- amino 2-chloro benzoic acid was coupled by Method G20. 3- methoxy benzaldehyde was converted to Fmoc- 3- chloro- phenylglycine by Method G62, and coupled to the aniline by Method G61. The Fmoc group was cleaved by Method G19. The appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S50

Compounds were synthesized using standard Fmoc solid phase methods on commercially available Fmoc- L- alanine- Wang resin (0.5 mmol/g). The Fmoc group was cleaved by Method G19. Commercially available 4- amino 2-chloro benzoic acid was coupled by Method G20. Fmoc- meta tyrosine was coupled to the aniline by Method G61. The Fmoc group was cleaved by Method G19. The appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S51

3-hydroxy aniline was coupled to commercially available Boc- d- serine by Method G3. The Boc group was removed by Method G1 and this amine was coupled to Compound A, Method G8. The *t*-butyl ester was removed by Method G11 and the acid coupled to the appropriate amino acid O-*t*-butyl ester (R) by Method G3. The final *t*-butyl ester was removed by Method G11, and the completed molecule was purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S52

The Boc group on Compound F, Method G75, was removed by Method G2 and furylacrylic acid was coupled to the amine after free basing, Method G2, by Method G3. The methyl ester was removed by Method G55 and the resulting acid coupled by Method G20 to the appropriate deprotected commercially available Fmoc protected amino acid Wang resin (0.5 mmol/g) (R). The completed molecule was worked up by Method G21.

Method S53

The methyl ester of Compound F, Method G75, was removed by Method G55 and the resulting acid coupled by Method G20 to commercially available L- asparagine *t*-butyl ester. The Boc group was removed by Method G1 and the appropriate carboxylic acid (R) was coupled by Method G3. After removing the final *t*-butyl ester by Method G11, the molecule was purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S54

The Boc group on Compound F, Method G75, was removed by Method 2G1 and furylacrylic acid was coupled to the amine after free basing, Method G2, by Method G3. The methyl

ester was removed by Method G55 and the resulting acid coupled by Method G20 to commercially available β- Boc- diaminopropionic acid methyl ester. The Boc group was removed by Method G1 and the appropriate carboxylic acid (R) was coupled by Method G3. After saponification, Method G4, the molecule was purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S55

The Boc group on Compound I, Method G75, was removed by Method G1 and 3-hydroxybenzoic acid was coupled to the amine after free basing, Method G2, by Method G3. The methyl ester was removed by Method G55 and the resulting acid coupled by Method G20 to commercially available L- tryptophan methyl ester. After saponification, Method G4, the molecule was purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S56

The Boc group on Compound H, Method G75, was removed by Method G1 and 3-hydroxybenzoic acid was coupled to the amine after free basing, Method G2, by Method G3. The methyl ester was removed by Method G55 and the resulting acid coupled by Method G20 to commercially available amino acid methyl ester (R). After saponification, Method G4, the molecule was purified by reverse phase HPLC verified by electrospray mass spectrometry and lyophilized to a powder.

Method S57

The Boc group on Compound H, Method G75, was removed by Method G1 and furylacrylic acid was coupled to the amine after free basing, Method G2, by Method G3. The methyl ester was removed by Method G55 and the resulting acid coupled by Method G20 to the appropriate commercially available amino acid methyl ester (R). The Boc group was removed by Method G1 if needed and after saponification, Method G4, the molecule was purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S58

The Boc group on Compound H, Method G75, was removed by Method G1 and 3-(2-thienyl)acrylic acid was coupled to the amine after free basing, Method G2, by Method G3. The methyl ester was removed by Method G55 and the resulting acid coupled by Method G20 to the appropriate commercially available amino acid methyl ester (R). The Boc group was removed by Method G1 if needed and after saponification, Method G4, the molecule was purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S59

The Boc group on Compound H, Method G75, was removed by Method 2G1 and furylacrylic acid was coupled to the amine after free basing, Method G2, by Method G3. The methyl ester was removed by Method G55 and the resulting acid coupled by Method G20 to commercially available β- Boc- diaminopropionic acid methyl ester. The Boc group was removed by Method G1

and the appropriate carboxylic acid (R) was coupled by Method G3. After saponification, Method G4, the molecule was purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S60

Compounds were synthesized using standard Fmoc solid phase methods on Fmoc- L-Lysine (alloc)- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L- Lys(alloc)- Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-N-ε-Alloc-L-lysine. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The Alloc group was removed by Method G35. The appropriate aldehyde (R) was coupled by Method G23. The completed molecule was worked up by Method G21.

Method S61

Compounds were synthesized using standard Fmoc solid phase methods on Fmoc- L-diamiopropionic acid (alloc)- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L- Dapa(alloc)-Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-N-β-Alloc-L-diaminopropionic acid. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The Alloc group was removed by Method G35. The appropriate aldehyde (R) was coupled by Method G23. The completed molecule was worked up by Method G21.

Method S62

The appropriate amine (R) was coupled to Compound A, Method G8, by Method G3. The *t*-butyl ester was removed by Method G11. The resulting acid was coupled by Method G3 to resin made by Method G34 using commercially available N-α-Fmoc-N-β-Alloc-L-diaminopropionic acid where the Fmoc group had been removed by Method G19. The completed molecule was worked up by Method G21.

Method S63

The appropriate amine (R) was coupled to Compound A, Method G8, by Method G3. The *t*-butyl ester was removed by Method G11. The resulting acid was coupled by Method G3 to commercially available Fmoc- L- asparagine(Trt)- Wang resin (0.5 mmol/g) where the Fmoc group had been removed by Method G19. The completed molecule was worked up by Method G21.

Method S64

The Boc group on Compound F, Method G75, was removed by Method G1 and reduced furylacrylic acid, Method G81, was coupled to the amine after free basing, Method G2, by Method G3. The methyl ester was removed by Method G55 and the resulting acid coupled by Method G20 to commercially available β- Boc- diaminopropionic acid methyl ester. The Boc group was removed by Method G1 and thiophene 2- carboxylic acid was coupled by Method G3. After saponification, Method G4, the molecule was purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S65

The Boc group on Compound F, Method G75, was removed by Method G1. 2- acetylfuran was converted to the methyl acrylic acid ethyl ester by Method G82 and after saponification by Method G80 was coupled to the amine after free basing, Method G2, by Method G3. The methyl ester was removed by Method G55 and the resulting acid coupled by Method G20 to commercially available β- Boc- diaminopropionic acid methyl ester. The Boc group was removed by Method G1 and thiophene 2- carboxylic acid was coupled by Method G3. After saponification, Method G4, the molecule was purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S66

The Boc group on Compound F, Method G75, was removed by Method G1. After 2-acetylfuran was converted to the methyl acrylic acid ethyl ester by Method G82, saponified by Method G80 and reduced by Method G81, it was coupled to the amine after free basing, Method G2, by Method G3. The methyl ester was removed by Method G55 and the resulting acid coupled by Method G20 to commercially available β- Boc- diaminopropionic acid methyl ester. The Boc group was removed by Method G1 and thiophene 2- carboxylic acid was coupled by Method G3. After saponification, Method G4, the molecule was purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S67

The Boc group on Compound F, Method G75, was removed by Method G1. Furylaldehyde was converted to the methyl acrylic acid ethyl ester by Method G83 and after saponification by Method G80 was coupled to the amine after free basing, Method G2, by Method G3. The methyl ester was removed by Method G55 and the resulting acid coupled by Method G20 to commercially available β- Boc- diaminopropionic acid methyl ester. The Boc group was removed by Method G1 and thiophene 2- carboxylic acid was coupled by Method G3. After saponification, Method G4 the molecule was purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S68

The Boc group on Compound F, Method G75, was removed by Method G1. After furylaldehyde was converted to the methyl acrylic acid ethyl ester by Method G83, saponified by Method G80 and reduced by Method G81, it was coupled to the amine after free basing, Method G2, by Method G3. The methyl ester was removed by Method G55 and the resulting acid coupled by Method G20 to commercially available β- Boc- diaminopropionic acid methyl ester. The Boc group was removed by Method G1 and thiophene 2- carboxylic acid was coupled by Method G3. After saponification, Method G4, the molecule was purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S69

Compounds were synthesized using standard Fmoc solid phase methods on the appropriate commercially available Fmoc- L- amino acid- Wang resin (0.5 mmol/g) (R). The Fmoc group was cleaved by Method G19. The commercially available 2, 6 dimethyl terephthalic acid was coupled by Method G20. 3- hydroxy benzylamine, Method G38, was coupled by Method G20. The completed molecule was worked up by Method G21 and correct stereochemistry was assigned by activity.

Method S70

Compounds were synthesized on resin made by Method G34 using commercially available N-a-Fmoc-N-b-Alloc-L-diaminopropionic acid. The Fmoc group was cleaved by Method G19. The commercially available 2, 6 dimethyl terephthalic acid was coupled by Method G20. 3- hydroxy benzylamine, Method G38, was coupled by Method G20. The Alloc group was removed by Method G35 and the appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21 and correct stereochemistry was assigned by activity.

Method S71

The Boc group on Compound F, Method G75, was removed by Method G1 and the appropriate carboxylic acid (R) was coupled to the amine after free basing, Method G2, by Method G3. The methyl ester was removed by Method G55 and the resulting acid coupled by Method G20 to commercially available β- Boc- diaminopropionic acid methyl ester. The Boc group was removed by Method G1 and thiophene 2- carboxylic acid was coupled by Method G3. After saponification, Method G4, the molecule was purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S72

Compounds were synthesized using standard Fmoc solid phase methods on commercially available Fmoc- L- tryptophan(Boc)- Wang resin (0.5 mmol/g). The Fmoc group was cleaved by Method G19. Commercially available 2- bromo terephthalic acid was protected with an Fmoc group by Method G6 and the resulting product was coupled by Method G20. The appropriate amine (R) was coupled by Method G22. The completed molecule was worked up by Method G21.

Method S73

Compounds were synthesized using standard Fmoc solid phase methods on commercially available Fmoc- L- alanine- Wang resin (0.5 mmol/g). The Fmoc group was cleaved by Method G19. Commercially available 2- bromo terephthalic acid was protected with an Fmoc group by Method G6 and the resulting product was coupled by Method G20. The appropriate amine (R) was coupled by Method G22. The completed molecule was worked up by Method G21.

Method S74

Compounds were synthesized using standard Fmoc solid phase methods on Fmoc- L-diamiobutyric acid (alloc)- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L- Daba(alloc)- Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-N-γ-Alloc-L-

diaminobutyric acid. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The Alloc group was removed by Method G35. The appropriate commercially available sulfonyl chloride (R) was coupled by Method G42. The completed molecule was worked up by Method G21.

Method S75

Compounds were synthesized using standard Fmoc solid phase methods on N-α-Fmoc-N-δ-Alloc-L-Ornithine- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L- Orn(alloc)- Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-N-δ-Alloc-L-Ornithine. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The Alloc group was removed by Method G35. The appropriate commercially available sulfonyl chloride (R) was coupled by Method G42. The completed molecule was worked up by Method G21.

Method S76

Compounds were synthesized using standard Fmoc solid phase methods on Fmoc- L-Lysine (alloc)- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L- Lys(alloc)- Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-N-ε-Alloc-L-lysine. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The Alloc group was removed by Method G35. The appropriate commercially available sulfonyl chloride (R) was coupled by Method G42. The completed molecule was worked up by Method G21.

Method S77

Compounds were synthesized using standard Fmoc solid phase methods on Fmoc- L-diamiobutyric acid (alloc)- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L- Daba(alloc)- Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-N-γ-Alloc-L-diaminobutyric acid. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The Alloc group was removed by Method G35. The appropriate commercially available chloroformate (R) was coupled by Method G43. The completed molecule was worked up by Method G21.

Method S78

Compounds were synthesized using standard Fmoc solid phase methods on N-α-Fmoc-N-δ-Alloc-L-Ornithine- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L- Orn(alloc)- Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-N-δ-Alloc-L-Ornithine. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The Alloc group was removed by Method G35. The appropriate commercially available chloroformate (R) was coupled by Method G43. The completed molecule was worked up by Method G21.

Method S79

Compounds were synthesized using standard Fmoc solid phase methods on Fmoc- L-Lysine (alloc)- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L- Lys(alloc)- Wang resin). The

resin was made by Method G34 using commercially available N-α-Fmoc-N-ε-Alloc-L-lysine. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The Alloc group was removed by Method G35. The appropriate commercially available chloroformate (R) was coupled by Method G43. The completed molecule was worked up by Method G21.

Method S80

Compounds were synthesized using standard Fmoc solid phase methods on commercially available Fmoc- L- asparagine(Trt)- Wang resin (0.5 mmol/g). The Fmoc group was cleaved by Method G19. Commercially available 2- bromo terephthalic acid was protected with an Fmoc group by Method G6 and the resulting product was coupled by Method G20. The appropriate amine (R) was coupled by Method G22. The completed molecule was worked up by Method G21.

Method S81

Compounds were synthesized on resin made by Method G34 using commercially available N-α-Fmoc-N-β-Alloc-L-diaminopropionic acid. The Fmoc group was cleaved by Method G19. Commercially available 2- bromo terephthalic acid was protected with an Fmoc group by Method G6 and the resulting product was coupled by Method G20. The appropriate amine (R) was coupled by Method G22. The completed molecule was worked up by Method G21.

Method S82

Compounds were synthesized using standard Fmoc solid phase methods on the appropriate commercially available Fmoc- amino acid p- alkoxybenzyl alcohol resin (R) (Wang resin) (0.5 mmol/g). The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S83

Compounds were synthesized using standard Fmoc solid phase methods on the appropriate commercially available Fmoc- amino acid p- alkoxybenzyl alcohol resin (R) (Wang resin) (0.5 mmol/g). The Fmoc group was cleaved by Method G19. Compound B, Method G12, was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S84

Compounds were synthesized using standard Fmoc solid phase methods on Fmoc- L-tryptophan(Boc)- Wang resin (0.5 mmol/g). The Fmoc group was cleaved by Method G19. Commercially available 4-amino 2-chlorobenzoic acid was coupled by Method G20. The resin was treated with an excess of 0.5M 4- nitrophenyl chloroformate and 0.5M DIPEA for 45 minutes. After twice washing the resin with THF/DCM, an excess of the appropriate amine (R) in 0.5M DIPEA/ DMF was added and the resin bubbled for 20 minutes. The completed molecule was worked up by Method G21.

Method S85

The appropriate amino acid (R) was converted to its methyl ester by Method G15. After free basing the amine by Method G2, Compound C, Method G13, was coupled to the amino acid methyl

ester by Method G3. After saponification, Method G4, the molecule was purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S86

3-hydroxyacetophenone was converted to the oxime by Method G70 and then hydrogenated by Method G38 to give the amine. This amine was then coupled to Compound A, Method G8, by Method G24. After removal of the *t*-butyl ester by Method G11, the acid was coupled to commercially available L-asparagine *t*-butyl ester by Method G24. The final *t*-butyl ester was removed by Method G11 and the completed molecule was purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S87

3-hydroxyacetophenone was converted to the oxime by Method G70 and then hydrogenated by Method G38 to give the amine. This amine was then coupled to Compound A, Method G8, by Method G24. After removal of the *t*-butyl ester by Method G11, the acid was coupled to commercially available L-tryptophan methyl ester by Method G24. The final methyl ester was removed by Method G4 and the completed molecule was purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S88

3-hydroxybenzaldehyde and ethyl magnesium bromide were converted to the ketone by Method G71. The ketone was then converted to the oxime by Method G70 and then hydrogenated by Method G38 to give the amine. This amine was then coupled to Compound A, Method G8, by Method G24. After removal of the *t*-butyl ester by Method G11, the acid was coupled to commercially available L-asparagine *t*-butyl ester by Method G24. The final *t*-butyl ester was removed by Method G11 and the completed molecule was purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S89

3-hydroxybenzaldehyde and ethyl magnesium bromide were converted to the ketone by Method G71. The ketone was then converted to the oxime by Method G70 and then hydrogenated by Method G38 to give the amine. This amine was then coupled to Compound A, Method G8, by Method G24. After removal of the *t*-butyl ester by Method G11, the acid was coupled to commercially available L-tryptophan methyl ester by Method G24. The final methyl ester was removed by Method G4 and the completed molecule was purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S90

3-hydroxybenzaldehyde and N-propyl magnesium bromide were converted to the ketone by Method G71. The ketone was then converted to the oxime by Method G70 and then hydrogenated by Method G38 to give the amine. This amine was then coupled to Compound A, Method G8, by Method G24. After removal of the *t*-butyl ester by Method G11, the acid was coupled to commercially available L-asparagine *t*-butyl ester by Method G24. The final *t*-butyl ester

was removed by Method G11 and the completed molecule was purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S91

3-hydroxybenzaldehyde and N-propyl magnesium bromide were converted to the ketone by Method G71. The ketone was then converted to the oxime by Method G70 and then hydrogenated by Method G38 to give the amine. This amine was then coupled to Compound A, Method G8, by Method G24. After removal of the *t*-butyl ester by Method G11, the acid was coupled to commercially available L-tryptophan methyl ester by Method G24. The final methyl ester was removed by Method G4 and the completed molecule was purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S92

The appropriate sulfonamide was synthesized by Method G93 using ammonia as the amine (R) and this product converted to the methyl ester by Method G15. Compound C, Method G13, was coupled to the sulfonamide methyl ester by Method G3. The finale methyl ester was removed by Method G4. The completed molecule was purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S93

Compounds were synthesized on commercially available Fmoc- L- asparagine(Trt)- Wang resin (0.5 mmol/g). The Fmoc group was removed by Method G19. The product of Method G65, with the exception that it was not resolved by Method G67, was Fmoc protected by Method G5 and the *t*-butyl ester removed by Method G11. This product was coupled to the resin by Method G20. The Fmoc group was removed by Method G19 and the appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S94

Compounds were synthesized on commercially available Fmoc- L- asparagine(Trt)- Wang resin (0.5 mmol/g). The Fmoc group was removed by Method G19. The Method S isomer of Method G65 was Fmoc protected by Method G5 and the *t*-butyl ester removed by Method G11. This product was coupled to the resin by Method G20. The Fmoc group was removed by Method G19 and the appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S95

Compounds were synthesized on commercially available Fmoc- L- alanine- Wang resin (0.5 mmol/g). The Fmoc group was removed by Method G19. The S isomer of Method G65 was Fmoc protected by Method G5 and the *t*-butyl ester removed by Method G11. This product was coupled to the resin by Method G20. The Fmoc group was removed by Method G19 and the appropriate carboxylic acid (R) was coupled by Method G20. The completed molecule was worked up by Method G21.

Method S96

Compounds were synthesized using standard Fmoc solid phase methods on commercially available Fmoc- L- tryptophan(Boc)- Wang resin (0.5 mmol/g). The Fmoc group was cleaved by Method G19. The appropriate commercially available di- acid (R) coupled by Method G20. 3-hydroxy benzylamine, Method G38, was coupled by Method G20. The completed molecule was worked up by Method G21 and correct stereochemistry was assigned by activity.

Method S97

Compounds were synthesized using standard Fmoc solid phase methods on commercially available Fmoc- L- asparagine(Trt)- Wang resin (0.5 mmol/g). The Fmoc group was cleaved by Method G19. The appropriate commercially available di- acid (R) coupled by Method G20. 3-hydroxy benzylamine, Method G38, was coupled by Method G20. The completed molecule was worked up by Method G21 and correct stereochemistry was assigned by activity.

Method S98

The product of Method G86 was coupled by Method G20 to the appropriate commercially available Fmoc- amino acid Wang resin (R) after removing the Fmoc group by Method G19. The completed molecule was worked up by Method G21 and correct stereochemistry was assigned by activity.

Method S99

3- hydroxymandelic acid was converted to its corresponding alcohol by Method G25 and coupled to the methyl ester of 4- hydroxy 2- chlorobenzoic acid, Method G15, by Method G26. The methyl ester removed by Method G4 and the carboxylic acid was coupled to L- asparagine *t*- butyl ester by Method G3. The final *t*- butyl ester was removed by Method G11 and the molecule was purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S100

3- hydroxymandelic acid was converted to its corresponding alcohol by Method G25 and coupled to the methyl ester of 4- hydroxy 2- chlorobenzoic acid, Method G15, by Method G26. The methyl ester removed by Method G4 and the carboxylic acid was coupled to L- alanine *t*- butyl ester by Method G3. The final *t*- butyl ester was removed by Method G11 and the molecule was purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S101

The methyl ester of 3-(3-hydroxyphenyl) propionic acid was made by Method G15 and converted to the aldehyde by Method G29. The oxazoline of 4- bromo 2-chloro benzoic acid was made by Method G30. The aldehyde was coupled to the bromide by Method G31 and the oxazoline converted to the ethyl ester by Method G32. After saponification by Method G4, the carboxylic acid was coupled to L- alanine methyl ester by Method G3. After saponification by Method G4, the molecule was purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S102

The methyl ester of 3-(3-hydroxyphenyl) propionic acid was made by Method G15 and converted to the aldehyde by Method G29. The oxazoline of 4- bromo 2-chloro benzoic acid was made by Method G30. The aldehyde was coupled to the bromide by Method G31 and the oxazoline converted to the ethyl ester by Method G32. The allylic alcohol was oxidized to the ketone by Method G27 and the ethyl ester was saponified by Method G4. The carboxylic acid was coupled to L- alanine methyl ester by Method G3; and after saponification by Method G4, the molecule was purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S103

The methyl ester of 4-hydroxy-2-chloro-benzoic acid was formed by Method G15. 1, 2-dibromoethane was coupled to the phenol by Method G51. The appropriate hydroxy phenol (R) was coupled by Method G52 and the methyl ester removed by Method G4. L- alanine- O-*t*-butyl ester was coupled be Method G3. The *t*-butyl ester was removed by Method G11 and the completed compound was purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S104

4-amino-2, 6-dichlorophenol was Boc protected by Method G44 and the phenol converted to its corresponding triflate by Method G45. The triflate was converted to a carboxylic acid methyl ester by Method G46. The Boc aniline was converted to the phenol by Method G47 and then the methyl ester removed by Method G48. The resulting carboxylic acid was then converted to its allyl ester by Method G49 (Compound G). 3- hydroxymandelic acid was converted to its corresponding alcohol by Method G25 and coupled to the phenol (Compound G) by Method G26. And the allyl ester removed by Method G50. The resulting benzoic acid was coupled to commercially available L-asparagine-O-*t*-butyl ester by Method G3. The *t*-butyl ester was removed by Method G11 without TES. The completed molecule was then concentrated *in vacuo*, purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S105

4-amino-2, 6-dichlorophenol was Boc protected by Method G44 and the phenol converted to its corresponding triflate by Method G45. The triflate was converted to a carboxylic acid methyl ester by Method G46. The Boc aniline was converted to the phenol by Method G47 and then the methyl ester removed by Method G48. The resulting carboxylic acid was then converted to its allyl ester by Method G49 (Compound G). 1, 3-dibromopropane was coupled to the phenol (Compound G) by Method G51. The 3-hydroxy phenol was coupled by Method G52 and the methyl ester removed by Method G4. The allyl ester removed by Method G50. The resulting benzoic acid was coupled to commercially available L-asparagine-O-*t*-butyl ester by Method G3. The *t*-butyl ester was removed by Method G11 without TES. The completed molecule was then concentrated *in vacuo*,

purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S106

4-amino-2, 6-dichlorophenol was Boc protected by Method G44 and the phenol converted to its corresponding triflate by Method G45. The triflate was converted to a carboxylic acid methyl ester by Method G46. The Boc aniline was converted to the phenol by Method G47 and then the methyl ester removed by Method G48. The resulting carboxylic acid was then converted to its allyl ester by Method G49 (Compound G). 1, 2-dibromopropane was coupled to the phenol (Compound G) by Method G51. The 3-hydroxy phenol was coupled by Method G52 and the methyl ester removed by Method G4. The allyl ester removed by Method G50. The resulting benzoic acid was coupled to commercially available L-asparagine-O-*t*-butyl ester by Method G3. The *t*-butyl ester was removed by Method G11 without TES. The completed molecule was then concentrated *in vacuo*, purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S107

4-amino-2, 6-dichlorophenol was Boc protected by Method G44 and the phenol converted to its corresponding triflate by Method G45. The triflate was converted to a carboxylic acid methyl ester by Method G46. The Boc aniline was converted to the phenol by Method G47 and then the methyl ester removed by Method G48. The resulting carboxylic acid was then converted to its allyl ester by Method G49 (Compound G). 1, 2-dibromopropane was coupled to the phenol (Compound G) by Method G51. The 3-hydroxy phenol was coupled by Method G52 and the methyl ester removed by Method G4. The allyl ester removed by Method G50. The resulting benzoic acid was coupled to commercially available L-alanine-O-*t*-butyl ester by Method G3. The *t*-butyl ester was removed by Method G11 without TES. The completed molecule was then concentrated *in vacuo*, purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S108

4-amino-2, 6-dichlorophenol was Boc protected by Method G44 and the phenol converted to its corresponding triflate by Method G45. The triflate was converted to a carboxylic acid methyl ester by Method G46. The Boc aniline was converted to the iodide by Method G54 and then the methyl ester removed by Method G55. This benzoic acid was then coupled to L-asparagine-O-*t*-butyl ester by Method G3. 3-hydroxybenzoic acid was converted to the hydroxamate by Method G56. The hydroxyl was protected as the *t*-butyl ether by Method G10 and the hydroxamate converted to the aldehyde by Method G57. The aldehyde was coupled to ethynyl magnesium bromide by Method G58 and the resulting product coupled to the above aryl iodide by Method G59. The alkyne was then reduced to the alkane by Method G60. The *t*-butyl ester and ether were removed by Method G11 without TES. The completed molecule was then concentrated *in vacuo*,

purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S109

4-amino-2, 6-dichlorophenol was Boc protected by Method G44 and the phenol converted to its corresponding triflate by Method G45. The triflate was converted to a carboxylic acid methyl ester by Method G46. The Boc aniline was converted to the iodide by Method G54 and then the methyl ester removed by Method G55. This benzoic acid was then coupled to L-asparagine-O-*t*-butyl ester by Method G3. 3-hydroxybenzoic acid was converted to the hydroxamate by Method G56. The hydroxyl was protected as the *t*-butyl ether by Method G10 and the hydroxamate converted to the aldehyde by Method G57. The aldehyde was coupled to ethynyl magnesium bromide by Method G58 and the resulting product coupled to the above aryl iodide by Method G59. The alkyne was then reduced to the alkane by Method G60. The *t*-butyl ester and ether were removed by Method G11. The completed molecule was then concentrated *in vacuo*, purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S110

3, 5-dimethyl-4-hydroxybenzaldehyde was coupled to ethynyl magnesium bromide by Method G58 and this product was coupled to 3-iodoanisole by Method G59. The alkynol was hydrogenated to the alkane by Method G38 except the product was purified by silica flash chromatography (3/6/1 hexane/DCM/Et_2O) to provide pure aryl alcohol. The alcohol was silyl protected by Method G18. The phenol converted to its corresponding triflate by Method G45. The triflate was converted to a carboxylic acid methyl ester by Method G46. The methyl ether and ester were removed by Method G55. The acid was coupled to L-asparagine-O-*t*-butyl ester by Method G3. The *t*-butyl ester was removed by Method G11 without TES and the silyl ether was removed in the same reaction by adding 3 equivalents of TBAF. The completed molecule was then concentrated *in vacuo*, purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S111

4-amino-2, 6-dichlorophenol was Boc protected by Method G44 and the phenol converted to its corresponding triflate by Method G45. The triflate was converted to a carboxylic acid methyl ester by Method G46. The Boc aniline was converted to the iodide by Method G54 and then the methyl ester removed by Method G55. This benzoic acid was then coupled to L-asparagine-O-*t*-butyl ester by Method G3. 3'-Hydroxyacetophenone was converted to the *t*-butyl ether using Method G10. G58 resulting alkyne coupled to the aryl iodide using Method G59. The alkyne was hydrogenated to the alkane using Method G60. Reductive removal of the benzylic alcohol, as well as cleavage of the *t*-butyl ether and ester groups was accomplished using Method G11 (containing excess TES). The crude product was isolated by concentrating *in vacuo*, purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S112

2, 6-Dichloro-4-methyl phenol was converted to the triflate according to Method G45. This triflate was carbonylated to the methyl ester using Method G46 and then converted to the aldehyde by Method G84. The aldehyde was treated with ethynyl magnesium bromide by Method G58 and the resulting alkyne coupled to 3-iodophenol using Method G59. The alkyne was hydrogenated to the alkane using Method G60 and the methyl ester was cleaved using Method G55. The resulting carboxylic acid was coupled to L-asparagine-O-*t*-butyl ester using Method G3. Cleavage of the *t*-butyl ester group was accomplished using Method G11 (containing no TES). The crude product was isolated by concentrating *in vacuo*, purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S113

2, 6-Dichloro-4-methyl phenol was converted to the triflate according to Method G45. This triflate was carbonylated to the methyl ester using Method G46 and then converted to the aldehyde by Method G84. 3-Iodophenol was silylated according to Method G18 to give O-*t*-butyl-dimethylsilyl-3-iodophenol. The aldehyde was treated with ethynyl magnesium bromide by Method G58 and the resulting alkyne coupled to O-*t*-butyl-dimethylsilyl-3-iodophenol using Method G59. The alkyne was hydrogenated to the alkane using Method G60. The resulting alcohol was converted to the methyl ether by Method G85 and the methyl ester was cleaved using Method G55. The resulting carboxylic acid was coupled to L- asparagine O-*t*-butyl ester using Method G3. The *t*-butyl ester was removed by Method G11 without TES and the silyl ether was removed in the same reaction by adding 3 equivalents of TBAF. The crude product was isolated by concentrating *in vacuo*, purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S114

2, 6-Dichloro-4-methyl phenol was converted to the triflate according to Method G45. This triflate was carbonylated to the methyl ester using Method G46 and then converted to the aldehyde by Method G84. 3-Iodophenol was silylated according to Method G18 to give O-*t*-butyl-dimethylsilyl-3-iodophenol. The aldehyde was treated with ethynyl magnesium bromide by Method G58 and the resulting alkyne coupled to O-*t*-butyl-dimethylsilyl-3-iodophenol using Method G59. The alkyne was hydrogenated to the alkane using Method G60 and the methyl ester was cleaved using Method G55. The resulting carboxylic acid was coupled to N-β-alloc-L-α, β-diaminopropionic acid methyl ester using Method G3 (adding an equivalent of DIPEA). The silyl ether was removed by Method G11 without TES with the addition of 3 equivalents of TBAF. The methyl ester was saponified using Method G4. The crude product was isolated by concentrating *in vacuo*, purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S115

2, 6-Dichloro-4-methyl phenol was converted to the triflate according to Method G45. This triflate was carbonylated to the methyl ester using Method G46 and then converted to the aldehyde by Method G84. 3-Iodophenol was silylated according to Method G18 to give O-*t*-butyl-dimethylsilyl-3-iodophenol. The aldehyde was treated with ethynyl magnesium bromide by Method G58 and the resulting alkyne coupled to O-*t*-butyl-dimethylsilyl-3-iodophenol using Method G59. The alkyne was hydrogenated to the alkane using Method G60 and the methyl ester was cleaved using Method G55. The resulting carboxylic acid was coupled to N-ε-Boc-L-lysine methyl ester using Method G3 (adding an equivalent of DIPEA). The methyl ester was saponified using Method G4 and the Boc group was removed by Method G11 without TES and the silyl ether was removed in the same reaction by adding 3 equivalents of TBAF The crude product was isolated by concentrating *in vacuo,* purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S116

3-Hydroxybenzoic acid was converted to the N-methoxy-N-methylamide using Method G56. The hydroxyl was protected as the *t*-butyl ether by Method G10. The N-methoxy-N-methylamide was reduced to the aldehyde by Method G57. The aldehyde was treated with ethynyl magnesium bromide by Method G58. 4-amino-2, 6-dichlorophenol was Boc protected by Method G44 and the phenol converted to its corresponding triflate by Method G45. The triflate was converted to a carboxylic acid methyl ester by Method G46. The Boc aniline was converted to the iodide by Method G54. The resulting aryl iodide was then coupled to the above alkyne by Method G59. The alkyne was hydrogenated to the alkane using Method G60. The methyl ester was cleaved using Method G55. The carboxylic acid was coupled to N-β-alloc-L-α, β-diaminopropionic acid methyl ester using Method G3 (adding an equivalent of DIPEA). The methyl ester was saponified using Method G4. The *t*-butyl ether was cleaved by using Method G11 (containing no TES). The crude product was isolated by concentrating *in vacuo,* purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S117

3-Hydroxybenzoic acid was converted to the N-methoxy-N-methylamide using Method G56. The hydroxyl was protected as the *t*-butyl ether by Method G10. The N-methoxy-N-methylamide was reduced to the aldehyde by Method G57. The aldehyde was treated with ethynyl magnesium bromide by Method G58. 4-amino-2, 6-dichlorophenol was Boc protected by Method G44 and the phenol converted to its corresponding triflate by Method G45. The triflate was converted to a carboxylic acid methyl ester by Method G46. The Boc aniline was converted to the iodide by Method G54. The resulting aryl iodide was then coupled to the above alkyne by Method G59. The alkyne was hydrogenated to the alkane using Method G60. The resulting alcohol was converted to the methyl ether by Method G85 and the methyl ester was cleaved using Method G55. The resulting carboxylic acid was coupled to L- asparagine-O-*t*-butyl ester using Method G3.

Cleavage of the *t*-butyl ester group was accomplished using Method G11 (containing no TES). The crude product was isolated by concentrating *in vacuo*, purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S118

4-amino-2, 6-dichlorophenol was Boc protected by Method G44 and the phenol converted to its corresponding triflate by Method G45. The triflate was converted to a carboxylic acid methyl ester by Method G46. The Boc aniline was converted to the iodide by Method G54. 3-Chlorobenzaldehyde was treated with ethynyl magnesium bromide by Method G58, and the resulting alkyne coupled to the above aryl iodide by Method G59. The alkyne was hydrogenated to the alkane using Method G60. The methyl ester was cleaved using Method G55. The carboxylic acid was coupled to N-β-alloc-L-α, β-diaminopropionic acid methyl ester using Method G3 (adding an equivalent of DIPEA). The methyl ester was saponified using Method G4. The crude product was isolated by concentrating *in vacuo*, purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S119

4-amino-2, 6-dichlorophenol was Boc protected by Method G44 and the phenol converted to its corresponding triflate by Method G45. The triflate was converted to a carboxylic acid methyl ester by Method G46. The Boc aniline was converted to the iodide by Method G54. 3-Chlorobenzaldehyde was treated with ethynyl magnesium bromide by Method G58, and the resulting alkyne coupled to the above aryl iodide by Method G59. The alkyne was hydrogenated to the alkane using Method G60. The methyl ester was removed by Method G55 and the resulting acid coupled by Method G20 to commercially available β- Boc- diaminopropionic acid methyl ester. The Boc group was removed by Method G1 and thiophene 2- carboxylic acid was coupled by Method G3. After saponification, Method G4, the molecule was purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S120

3-Hydroxybenzoic acid was converted to the N-methoxy-N-methylamide using Method G56. The hydroxyl was protected as the *t*-butyl ether by Method G10. The N-methoxy-N-methylamide was reduced to the aldehyde by Method G57. The aldehyde was treated with ethynyl magnesium bromide by Method G58. 4-amino-2, 6-dichlorophenol was Boc protected by Method G44 and the phenol converted to its corresponding triflate by Method G45. The triflate was converted to a carboxylic acid methyl ester by Method G46. The Boc aniline was converted to the iodide by Method G54. The resulting aryl iodide was then coupled to the above alkyne by Method G59. The alkyne was hydrogenated to the alkane using Method G60. The methyl ester was removed by Method G55 and the resulting acid coupled by Method G20 to commercially available β- Boc-diaminopropionic acid methyl ester. The Boc group was removed by Method G1 and thiophene 2-carboxylic acid was coupled by Method G3. After saponification, Method G4, the molecule was

purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S121

4-amino-2, 6-dichlorophenol was Boc protected by Method G44 and the phenol converted to its corresponding triflate by Method G45. The triflate was converted to a carboxylic acid methyl ester by Method G46. The Boc aniline was converted to the iodide by Method G54. 3-Chlorobenzaldehyde was treated with ethynyl magnesium bromide by Method G58, and the resulting alkyne coupled to the above aryl iodide by Method G59. The alkyne was hydrogenated to the alkane using Method G60. The methyl ester was removed by Method G55 and the resulting acid coupled by Method G20 to commercially available N-ε-Boc-L-lysine methyl ester using Method G3 (adding an equivalent of DIPEA). The methyl ester was saponified using Method G4 and the Boc group was removed by Method G11 (containing no TES). The crude product was isolated by concentrating *in vacuo*, purified by reverse phase HPLC, verified by electrospray mass spectrometry and lyophilized to a powder.

Method S122

Compounds were synthesized using standard Fmoc solid phase methods on commercially available Fmoc- glycine- Wang resin (0.5 mmol/g). The Fmoc group was cleaved by Method G19. The α glycine α carbon was alkylated with the appropriate commercially available bromide or chloride by Method G36 resulting in the corresponding racemic amino acid. Compound E was coupled to the resin by Method G37 and the completed molecule was worked up by Method G21.

Method S123

Compounds were synthesized using standard Fmoc solid phase methods on Fmoc- L-Aspartic acid (allyl)- p- alkoxybenzyl alcohol resin (0.5 mmol/g). The resin was made by Method G34 using commercially available N-α-Fmoc-β-Allyl-L-aspartic acid. The Fmoc group was cleaved by Method G19. Compound E was coupled to the resin by Method G37. The Allyl group was removed by Method G39. The appropriate aniline (R) was coupled by Method G40. The completed molecule was worked up by Method G21.

Method S124

Compounds were synthesized using standard Fmoc solid phase methods on Fmoc- L-aspartic acid (allyl)- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L- asp(alloc)- Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-β-Allyl-L-aspartic acid. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The allyl group was removed by Method G39. The appropriate amine (R) was coupled by Method G41. The completed molecule was worked up by Method G21.

Method S125

Compounds were synthesized using standard Fmoc solid phase methods on Fmoc- L-glutamic acid (allyl)- p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L- glu(alloc)- Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-β-Allyl-L-glutamic

acid. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The allyl group was removed by Method G39. The appropriate amine (R) was coupled by Method G41. The completed molecule was worked up by Method G21.

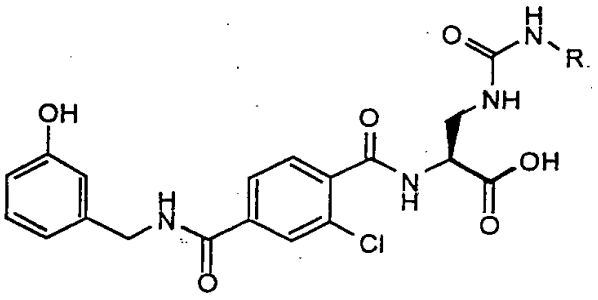
Method S126

Compounds were synthesized using standard Fmoc solid phase methods on N-α-Fmoc-O-trityl-L-serine-p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L- Ser(trityl)- Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-O-trityl-L-serine. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The trityl group was removed by Method G72. The appropriate amine (R) was coupled by Method G73. The completed molecule was worked up by Method G21.

Method S127

Compounds were synthesized using standard Fmoc solid phase methods on N-α-Fmoc-O-trityl-L-threonine-p- alkoxybenzyl alcohol resin (0.5 mmol/g) (Fmoc- L- thr(trityl)- Wang resin). The resin was made by Method G34 using commercially available N-α-Fmoc-O-trityl-L-serine. The Fmoc group was cleaved by Method G19. Compound C, Method G13, was coupled by Method G20. The trityl group was removed by Method G72. The appropriate amine (R) was coupled by Method G73. The completed molecule was worked up by Method G21.

Examples 1-39

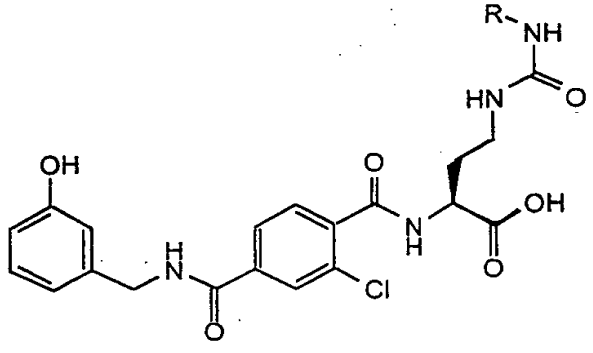


Examples 1-39 were synthesized by Method S1.

Example #	R group
1	2-isopropylphenyl isocyanate
2	phenethyl isocyanate
3	1-napthyl isocyanate
4	(S)-(-)-a-methylbenzyl isocyanate
5	cyclohexyl isocyanate
6	ethoxycarbonyl isocyanate
7	isopropyl isocyanate
8	trans-2-phenylcyclopropyl isocyanate
9	1-adamantyl isocyanate
10	phenyl isocyante
11	4-(methylthio)phenyl isocyanate

12	3-(methylthio)phenyl isocyanate
13	3-ethoxycarbonylphenyl isocyanate
14	4-ethoxycarbonylphenyl isocyanate
15	4-fluorophenyl isocyanate
16	2-fluorophenyl isocyanate
17	2-(trifluoromethoxy)phenyl isocyanate
18	3-fluorophenyl isocyanate
19	3-bromophenyl isocyanate
20	4-methoxyphenyl isocyanate
21	4-isopropylphenyl isocyanate
22	3-(2-hydroxy)ethyl phenyl isocyanate
23	4-ethylphenyl isocyanate
24	2-nitrophenyl isocyanate
25	3-nitrophenyl isocyanate
26	4-nitrophenyl isocyanate
27	3-cyanophenyl isocyanate
28	4-trifluoromethyl isocyanate
29	3-trifluoromethyl isocyanate
30	2-trifluoromethyl isocyanate
31	3-methylphenyl isocyanate
32	4-chlorophenyl isocyanate
33	3-chlorophenyl isocyanate
34	3-chloro-4-methylphenyl isocyanate
35	3-ethylphenyl isocyanate
36	allyl isocyanate
37	(S)-(-)-a-methylbenzyl isocyanate
38	cyclohexyl isocyanate
39	trans-2-phenylcyclopropyl isocyanate

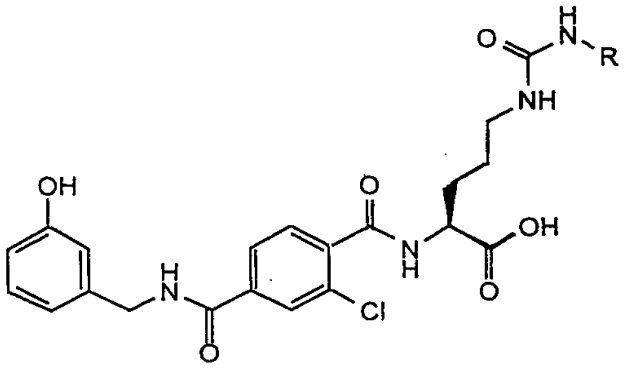
Examples 40-43



Examples 40-43 were synthesized by Method S2.

Example #	R group
40	benzyl isocyanate
41	ethoxycarbonyl isocyanate
42	2-chloro-6-methylphenyl isocyanate
43	ethoxycarbonyl isocyanate

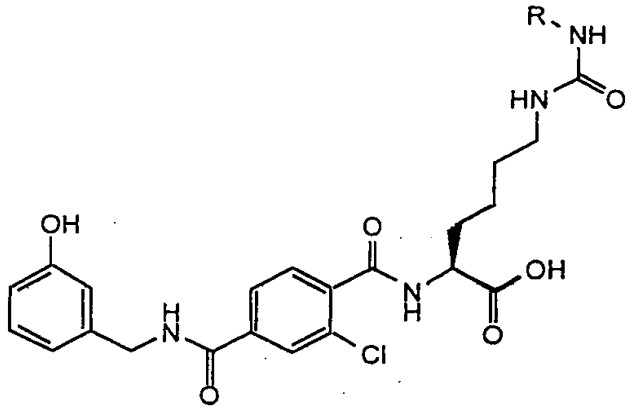
Examples 44-62



Examples 44-62 were synthesized by Method S3.

Example #	R group
44	phenethyl isocyanate
45	isopropyl isocyanate
46	cyclohexyl isocyanate
47	3-ethoxycarbonylphenyl isocyanate
48	4-ethoxycarbonylphenyl isocyanate
49	4-fluorophenyl isocyanate
50	2-fluorophenyl isocyanate
51	3-fluorophenyl isocyanate
52	4-methoxyphenyl isocyanate
53	4-isopropylphenyl isocyanate
54	3-(2-hydroxyethyl)phenyl isocyanate
55	2-nitrophenyl isocyanate
56	4-nitrophenyl isocyanate
57	3-cyanophenyl isocyanate
58	3-methylphenyl isocyanate
59	4-chlorophenyl isocyanate
60	3-chloro-4-methylphenyl isocyanate
61	2-chloro-6-methylphenyl isocyanate
62	4-ethylphenyl isocyanate

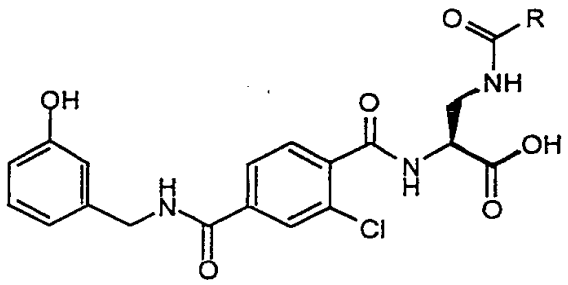
Examples 63-71



Examples 63-71 were synthesized by Method S4.

Example #	R group
63	phenethyl isocyanate
64	isopropyl isocyanate
65	benzyl isocyanate
66	propyl isocyanate
67	ethoxycarbonyl isocyanate
68	ethyl 2-isocyanato-4-methylvalerate
69	(S)-(-)-a-methylbenzyl isocyanate
70	benzensulfonyl isocyanate
71	benzyl isocyanate

Examples 72-95

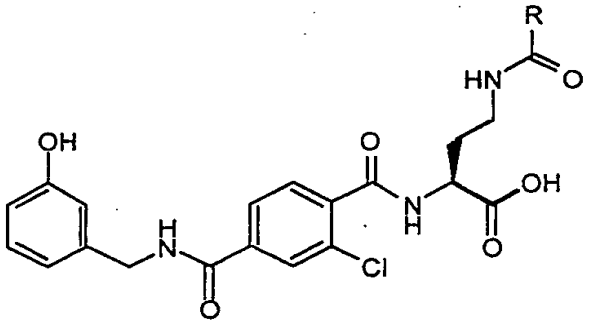


Examples 72-95 were synthesized by Method S5.

Example #	R group
72	3-methylindene-2-carboxylic acid
73	3-methylbenzofuran-2-carboxylic acid
74	4-Oxo-4, 5, 6, 7-tetrahydro-benzofuran-3-carboxylic acid
75	1, 2, 5-Trimethyl-1H-pyrrole-3-carboxylic acid
76	4-Methyl-[1, 2, 3]thiadiazole-5-carboxylic acid

77	4-Phenyl-[1, 2, 3]thiadiazole-5-carboxylic acid
78	3-chloro-2thiophenecarboxylic acid
79	3, 5-Dimethyl-isoxazole-4-carboxylic acid
80	3-methyl-2-furoic acid
81	3-bromothiophene-2-carboxylic acid
82	2-furoic acid
83	3-furoic acid
84	2-thiophene carboxylic acid
85	3- thiophenecarboxylic acid
86	5- chloro 2- thiophene carboxylic acid
87	5- bromo 2- thiophene carboxylic acid
88	indole 5- carboxylic acid
89	indole 4- carboxylic acid
90	indole 6- carboxylic acid
91	benzoic acid
92	cyclohexyl carboxylic acid
93	acetic acid
94	isonipecotic acid
95	pipecolinic acid

Examples 96-113

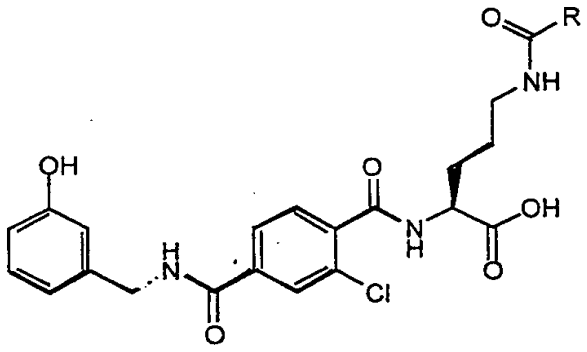


Examples 96-113 were synthesized by Method S6.

Example #	R group
96	3, 4, 5-trimethoxybenzoic acid
97	propionic acid
98	cyclopropyl carboxylic acid
99	trimethyl acetic acid
100	1, 2, 5-Trimethyl-1H-pyrrole-3-carboxylic acid
101	3-Chloro-4-methanesulfonyl-thiophene-2-carboxylic acid
102	4-Methyl-[1, 2, 3]thiadiazole-5-carboxylic acid
103	4-Phenyl-[1, 2, 3]thiadiazole-5-carboxylic acid

104	4-Bromo-2-ethyl-5-methyl-2H-pyrazole-3-carboxylic acid
105	3-chlorothiophene-2-carboxylic acid
106	3, 5-Dimethyl-isoxazole-4-carboxylic acid
107	5-Methyl-2-phenyl-2H-[1, 2, 3]triazole-4-carboxylic acid
108	3-methyl-2-furoic acid
109	3-bromothiophene-2-carboxylic acid
110	benzoic acid
111	cyclohexyl carboxylic acid
112	acetic acid
113	none

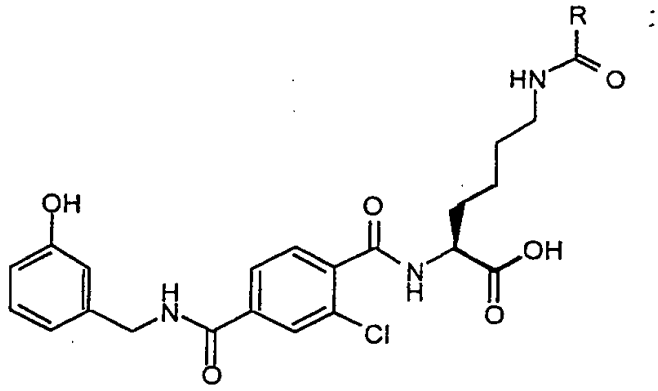
Examples 114-126



Examples 114-126 were synthesized by Method S7.

Example #	R group
114	trimethyl acetic acid
115	3-Chloro-benzo[b]thiophene-2-carboxylic acid
116	3-chlorothiophene-2-carboxylic acid
117	3, 5-Dimethyl-isoxazole-4-carboxylic acid
118	3-bromothiophene-2-carboxylic acid
119	3-methylindene-2-carboxylic acid
120	4-Oxo-4, 5, 6, 7-tetrahydro-benzofuran-3-carboxylic acid
121	3-Chloro-4-methanesulfonyl-thiophene-2-carboxylic acid
122	4-Methyl-[1, 2, 3]thiadiazole-5-carboxylic acid
123	4-Bromo-2-ethyl-5-methyl-2H-pyrazole-3-carboxylic acid
124	benzoic acid
125	cyclohexane carboxylic acid
126	acetic acid

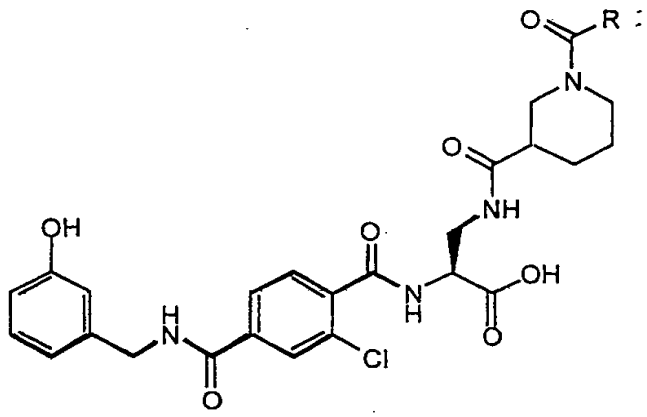
Examples 127-144



Examples 127-144 were synthesized by Method S8.

Example #	R group
127	3, 4, 5-trimethoxybenzoic acid
128	isovaleric acid
129	propionic acid
130	cyclopropyl carboxylic acid
131	4-acetyl-3, 5-dimethyl-2-pyrrolecarboxylic acid
132	3-methylindene-2-carboxylic acid
133	4-Oxo-4, 5, 6, 7-tetrahydro-benzofuran-3-carboxylic acid
134	1, 2, 5-Trimethyl-1H-pyrrole-3-carboxylic acid
135	3-Chloro-4-methanesulfonyl-thiophene-2-carboxylic acid
136	4-Methyl-[1, 2, 3]thiadiazole-5-carboxylic acid
137	4-Phenyl-[1, 2, 3]thiadiazole-5-carboxylic acid
138	4-Bromo-2-ethyl-5-methyl-2H-pyrazole-3-carboxylic acid
139	3-chlorothiophene-2-carboxylic acid
140	3, 5-Dimethyl-isoxazole-4-carboxylic acid
141	5-Methyl-2-phenyl-2H-[1, 2, 3]triazole-4-carboxylic acid
142	3-bromothiophene-2-carboxylic acid
143	benzoic acid
144	cyclohexyl carboxylic acid

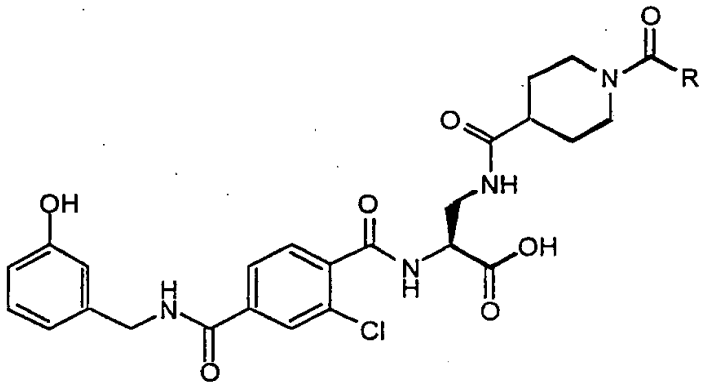
Examples 145-147



Examples 145-147 were synthesized by Method S9.

Example #	R group
145	propionic acid
146	acetic acid
147	none

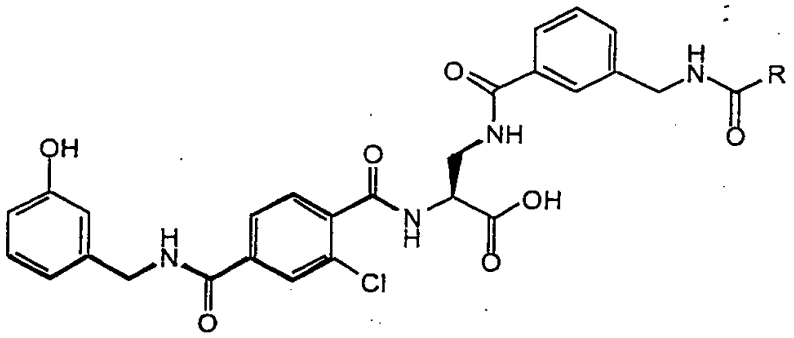
Examples 148-150



Examples 148-150 were synthesized by Method S10.

Example #	R group
148	propionic acid
149	butyric acid
150	acetic acid

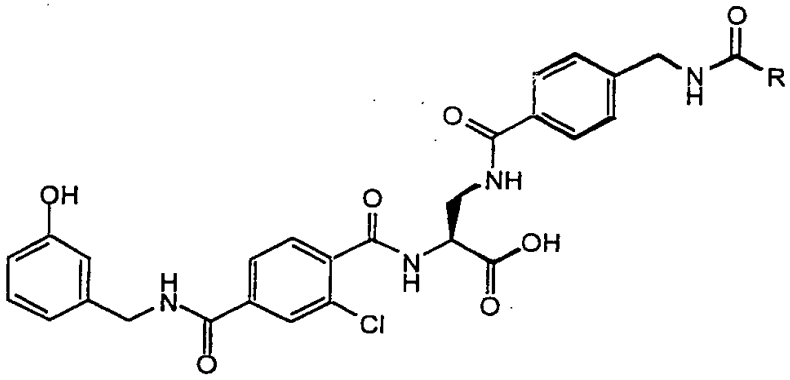
Examples 151-154



Examples 151-154 were synthesized by Method S11.

Example #	R group
151	propionic acid
152	butyric acid
153	acetic acid
154	none

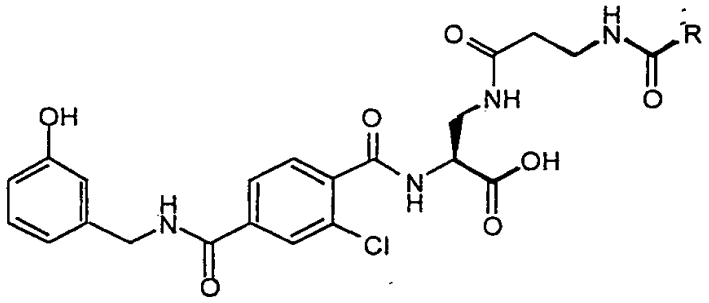
Examples 155-158



Examples 155-158 were synthesized by Method S12.

Example #	R group
155	propionic acid
156	butyric acid
157	acetic acid
158	none

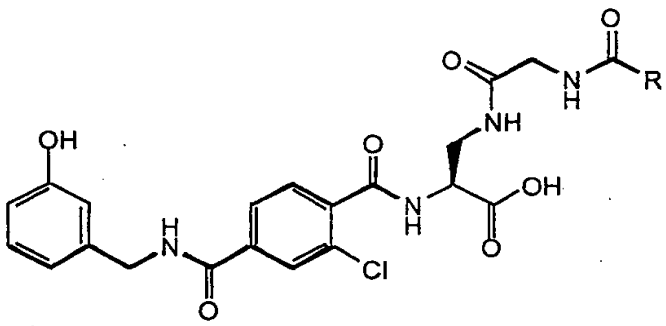
Examples 159-161



Examples 159-161 were synthesized by Method S13.

Example #	R group
159	propionic acid
160	acetic acid
161	none

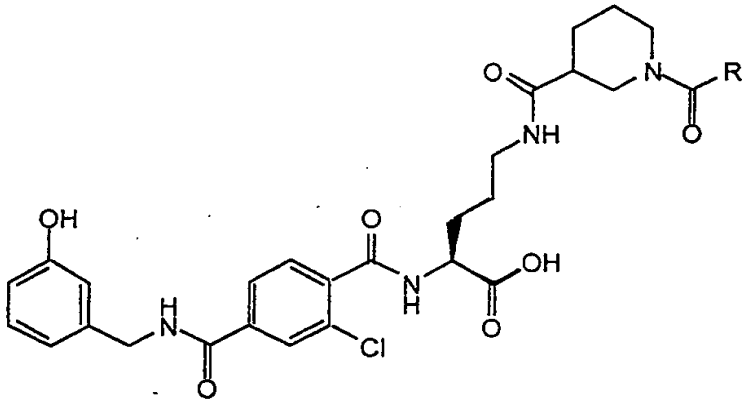
Examples 162-163



Examples 162-163 were synthesized by Method S14.

Example #	R group
162	acetic acid
163	none

Examples 164-167

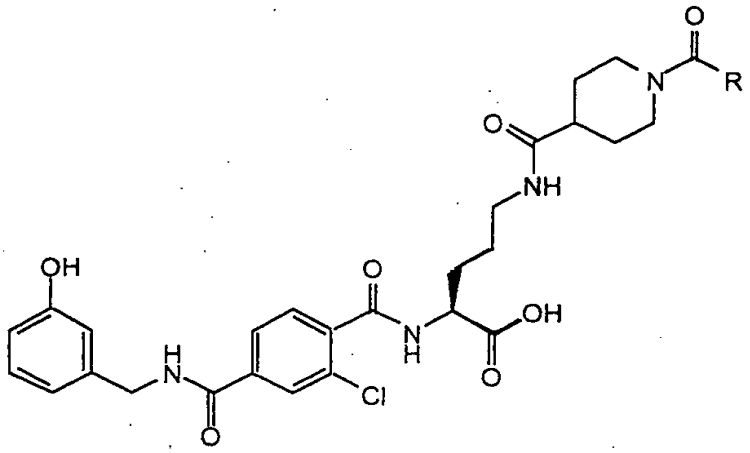


Examples 164-167 were synthesized by Method S15.

Example #	R group

164	propionic acid
165	butyric acid
166	acetic acid
167	none

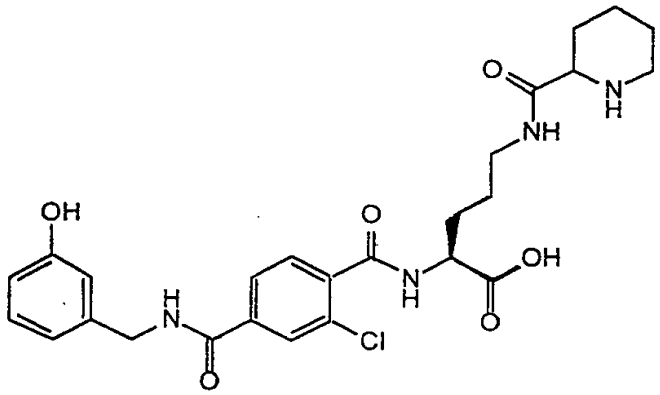
Examples 168-171



Examples 168-171 were synthesized by Method S16.

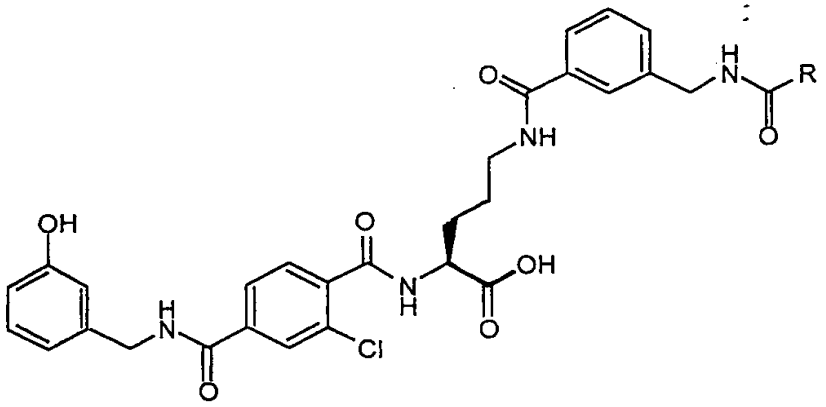
Example #	R group
168	propionic acid
169	butyric acid
170	acetic acid
171	none

Example 172



Example 172 was synthesized by Method S17.

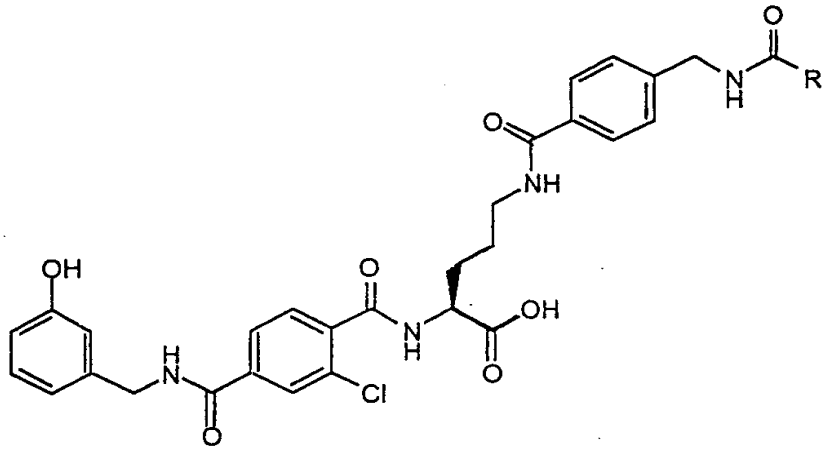
Examples 173-176



Examples 173-176 were synthesized by Method S18.

Example #	R group
173	propionic acid
174	butyric acid
175	acetic acid
176	none

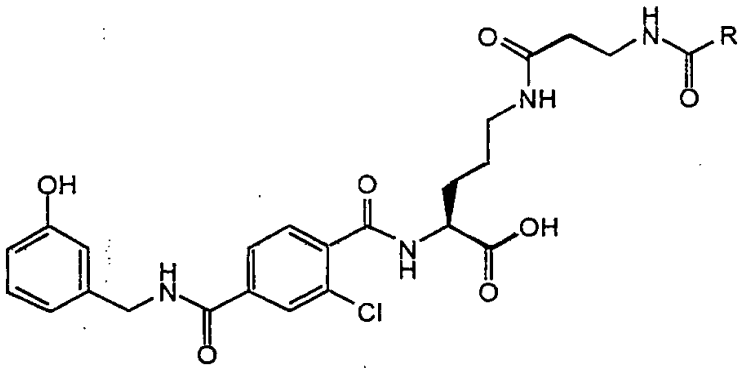
Examples 177-180



Examples 177-180 were synthesized by Method S19.

Example #	R group
177	propionic acid
178	butyric acid
179	acetic acid
180	none

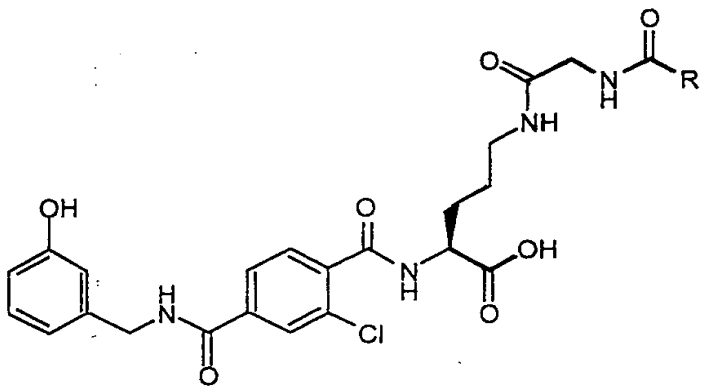
Examples 181-184



Examples 181-184 were synthesized by Method S20.

Example #	R group
181	propionic acid
182	butyric acid
183	acetic acid
184	none

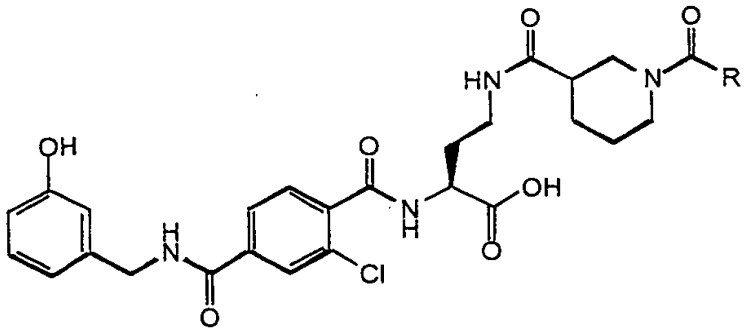
Examples 185-188



Examples 185-188 were synthesized by Method S21.

Example #	R group
185	propionic acid
186	butyric acid
187	acetic acid
188	none

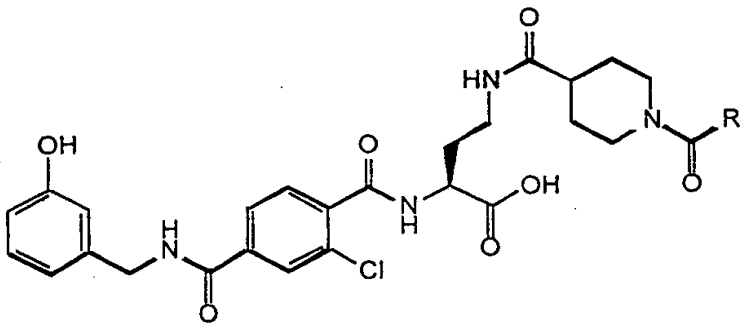
Examples 189-192



Examples 189-192 were synthesized by Method S22.

Example #	R group
189	propionic acid
190	butyric acid
191	acetic acid
192	none

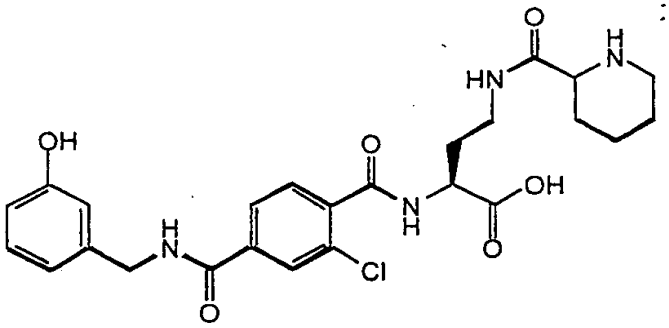
Examples 193-196



Examples 193-196 were synthesized by Method S23.

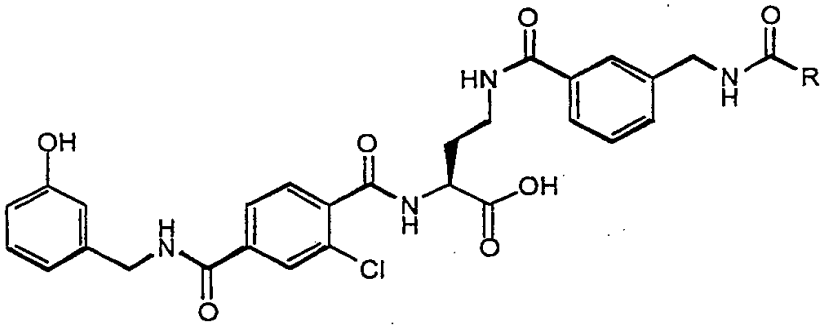
Example #	R group
193	propionic acid
194	butyric acid
195	acetic acid
196	none

Example 197



Example 197 was synthesized by Method S24.

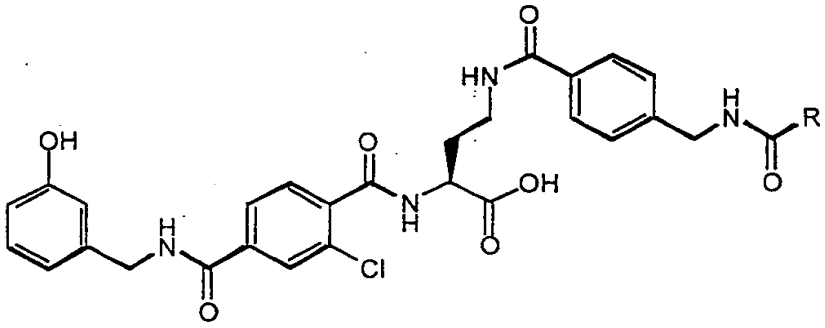
Examples 198-201



Examples 198-201 were synthesized by Method S25.

Example #	R group
198	propionic acid
199	butyric acid
200	acetic acid
201	none

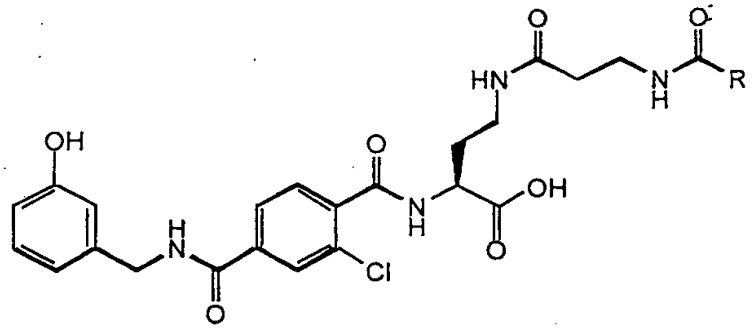
Examples 202-205



Examples 202-205 were synthesized by Method S26.

Example #	R group
202	propionic acid
203	butyric acid
204	acetic acid
205	none

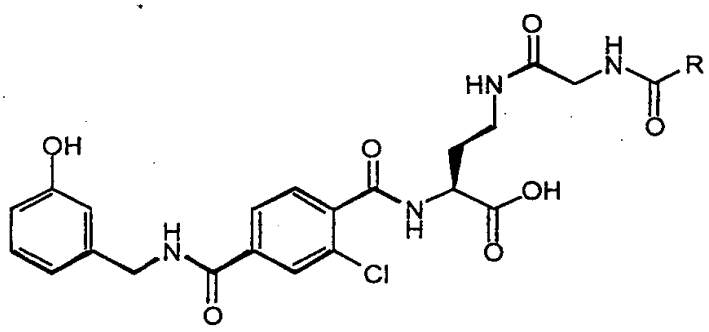
Examples 206-209



Examples 206-209 were synthesized by Method S27.

Example #	R group
206	propionic acid
207	butyric acid
208	acetic acid
209	none

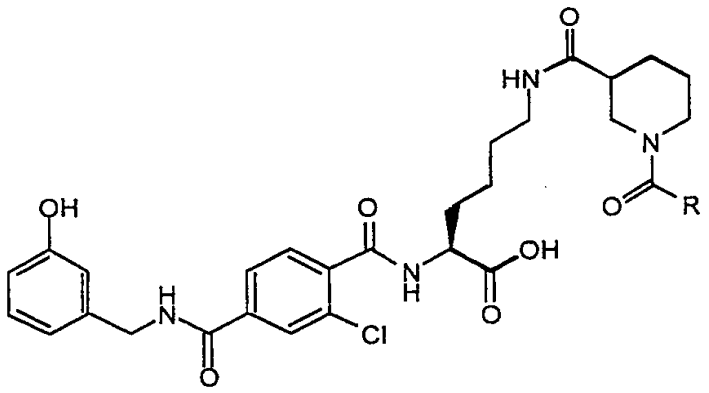
Examples 210-213



Examples 210-213 were synthesized by Method S28.

Example #	R group
210	propionic acid
211	butyric acid
212	acetic acid
213	none

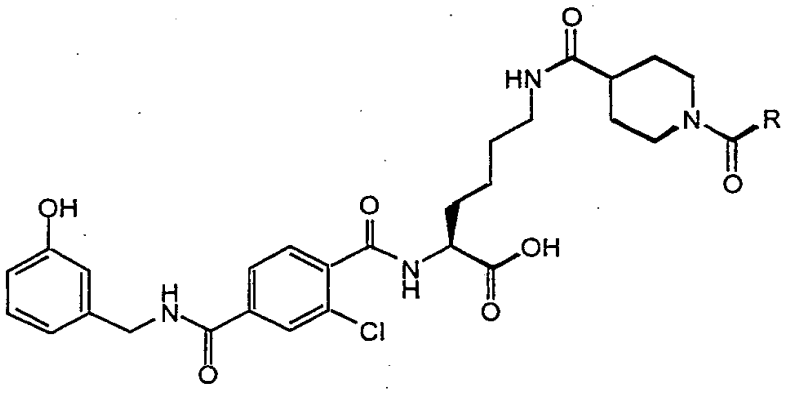
Examples 214-217



Examples 214-217 were synthesized by Method S29.

Example #	R group
214	propionic acid
215	butyric acid
216	acetic acid
217	none

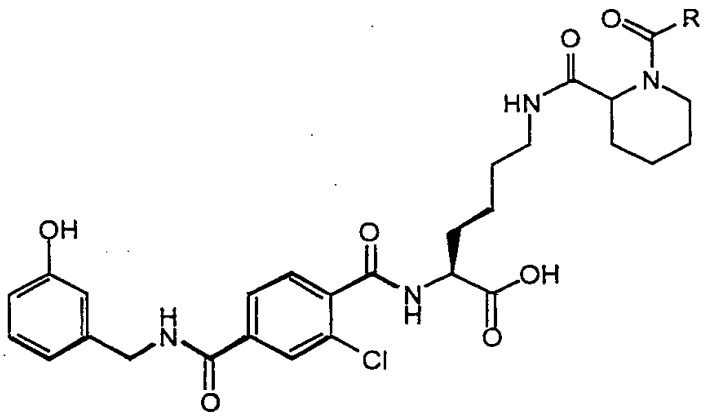
Examples 218-221



Examples 218-221 were synthesized by Method S30.

Example #	R group
218	propionic acid
219	butyric acid
220	acetic acid
221	none

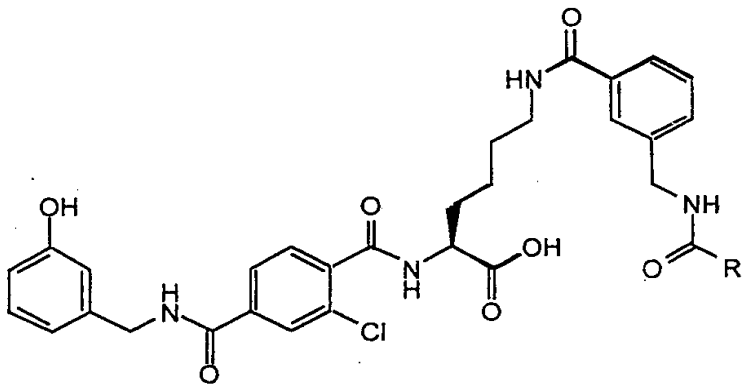
Examples 222-223



Examples 222-223 were synthesized by Method S31.

Example #	R group
222	acetic acid
223	none

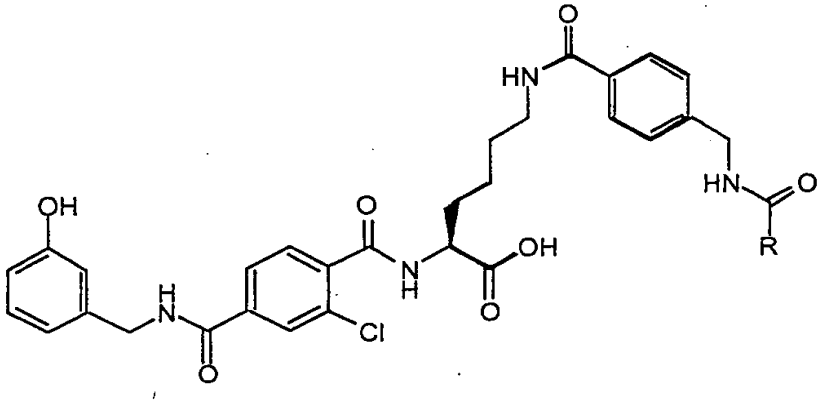
Examples 224-225



Examples 224-225 were synthesized by Method S32.

Example #	R group
224	propionic acid
225	none

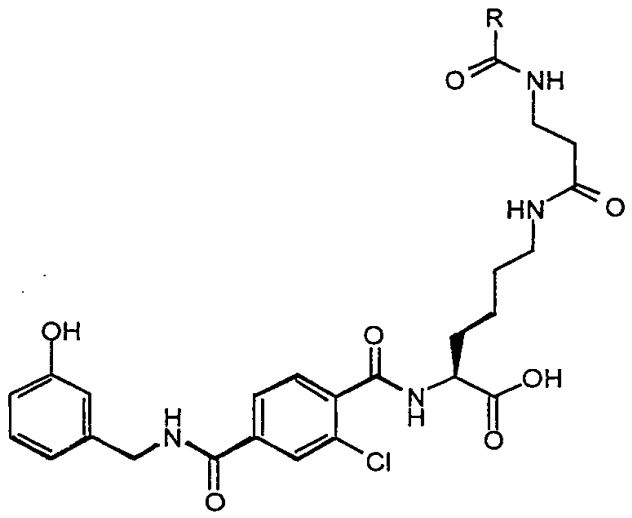
Examples 226-227



Examples 226-227 were synthesized by Method S33.

Example #	R group
226	acetic acid
227	none

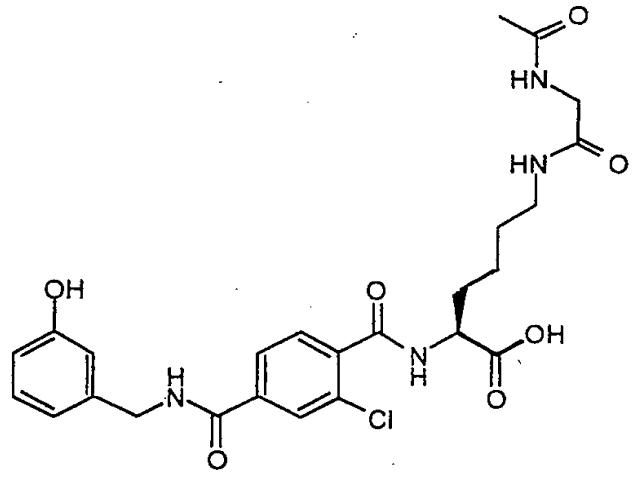
Examples 228-229



Examples 228-229 were synthesized by Method S34.

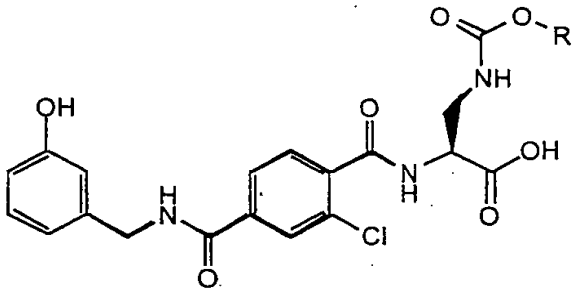
Example #	R group
228	acetic acid
229	none

Example 230



Example 230 was synthesized by Method S35.

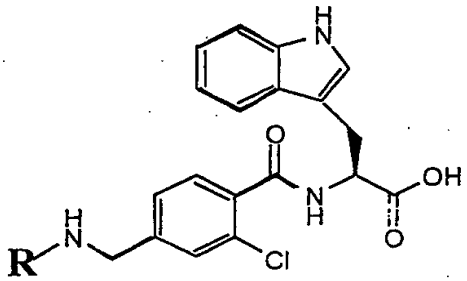
Examples 231-237



Examples 231-237 were synthesized by Method S36.

Example #	R group
231	propyl chloroformate
232	benzyl chloroformate
233	isopropyl chloroformate
234	methyl chloroformate
235	ethyl chloroformate
236	butyl chloroformate
237	3- butenyl chloroformate

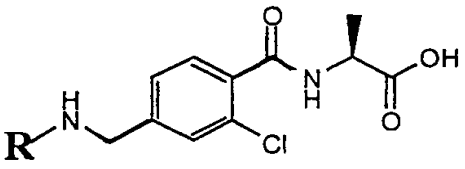
Examples 238-240



Examples 238-240 were synthesized by Method S37.

Example #	R group
238	3- hydroxy benzoic acid
239	2- hydroxy cinnamic acid
240	3- hydroxy benzoic acid

Examples 241-245

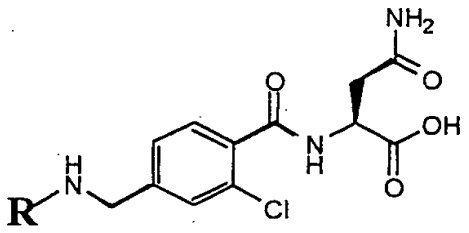


Examples 241-245 were synthesized by Method S38.

Example #	R group
241	3- hydroxy benzoic acid
242	2- hydroxy cinnamic acid

243	3- chloro benzoic acid
244	indole 5- carboxylic acid
245	3- (2- thienyl)acrylic acid

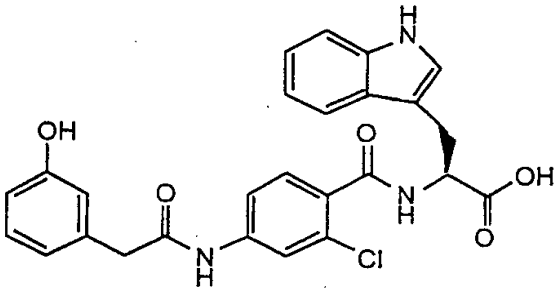
Examples 246-253



Examples 246-253 were synthesized by Method S39.

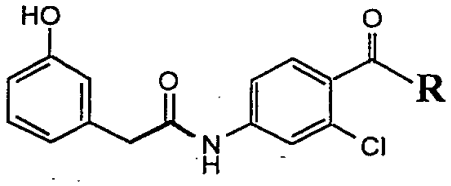
Example #	R group
246	3- chlorobenzoic acid
247	3 - (2 - thienyl)acrylic acid
248	2 - furanacrylic acid
249	3- hydroxy benzoic acid
250	indole 5-carboxylic acid
251	benzofuran 5-carboxylic acid
252	benzofuran 4-carboxylic acid
253	indole 6-carboxylic acid

Examples 254



Examples 254 were synthesized by Method S40.

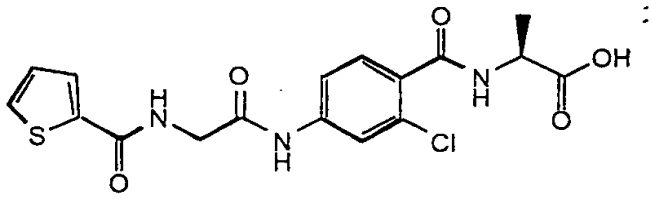
Examples 255-256



Examples 255-256 were synthesized by Method S41.

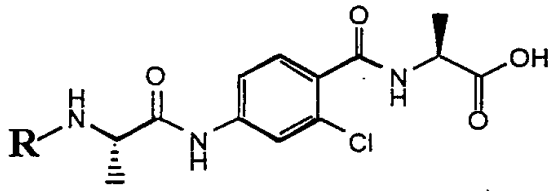
Example #	R group
255	L - Ala
256	L - Thr

Example 257



Example 257 was synthesized by Method S42.

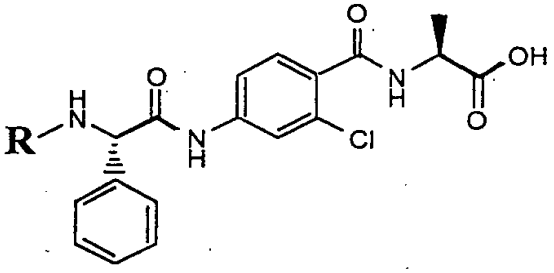
Examples 258-259



Examples 258-259 were synthesized by Method S43.

Example #	R group
258	2-thiophene carboxylic acid
259	3-hydroxybenzoic acid

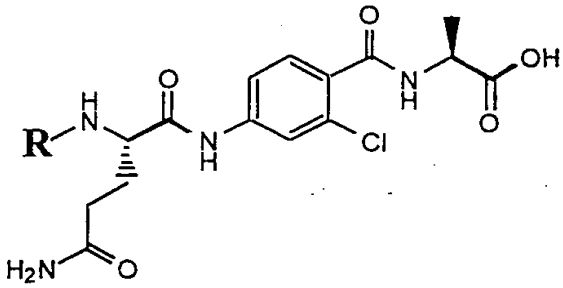
Examples 260-261



Examples 260-261 were synthesized by Method S44.

Example #	R group
260	3-hydroxybenzoic acid
261	2-thiophene carboxylic acid

Examples 262-263

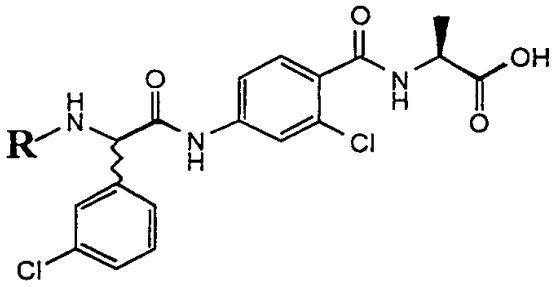


Examples 262-263 were synthesized by Method S45.

Example #	R group
262	benzoic acid

263	2-thiophene carboxylic acid

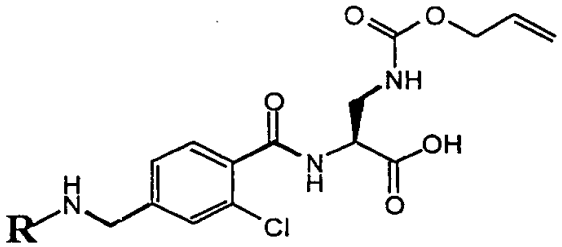
Examples 264-265



Examples 264-265 were synthesized by Method S46.

Example #	R group
264	3-hydroxybenzoic acid
265	2-thiophene carboxylic acid

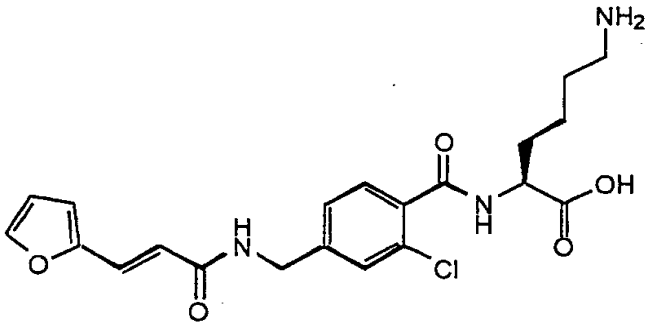
Examples 266-267



Examples 266-267 were synthesized by Method S47.

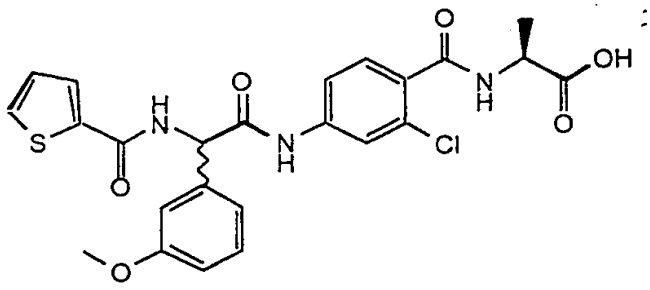
Example #	R group
266	3-(2-thienyl)-acrylic acid
267	furylacrylic acid

Example 268



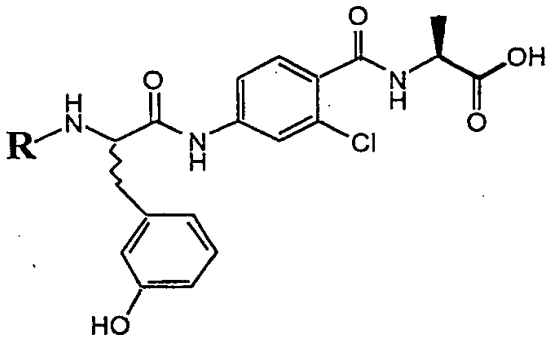
Example 268 was synthesized by Method S48.

Example 269



Example 269 was synthesized by Method S49.

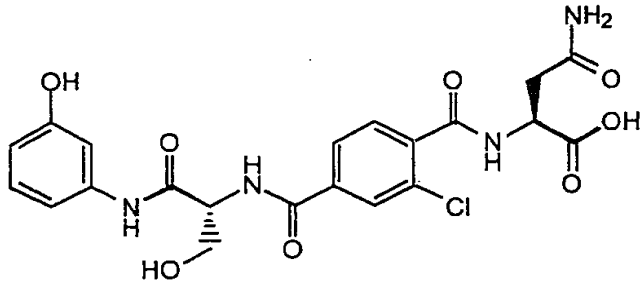
Examples 270-271



Examples 270-271 were synthesized by Method S50.

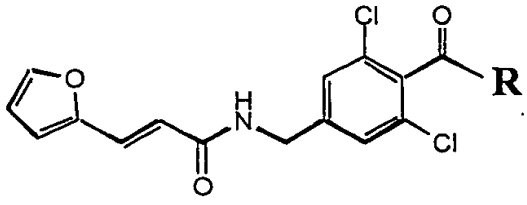
Example #	R group
270	3- hydroxybenzoic acid
271	2- thiophene carboxylic acid

Example 272



Example 272 was synthesized by Method S51.

Examples 273-275

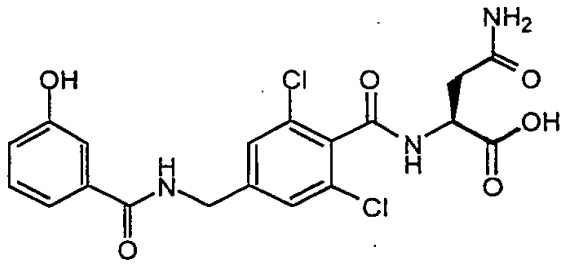


Examples 273-275 were synthesized by Method S52.

Example #	R group

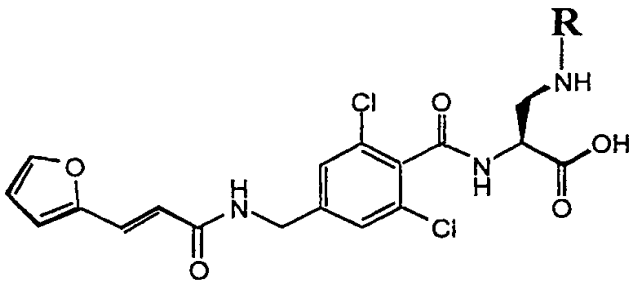
273	L- Ala
274	L- Asn
275	L- diaminopropionic acid (alloc)

Example 276



Example 276 was synthesized by Method S53.

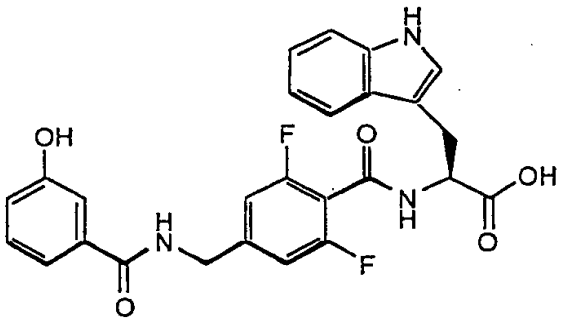
Examples 277-282



Examples 277-282 were synthesized by Method S54.

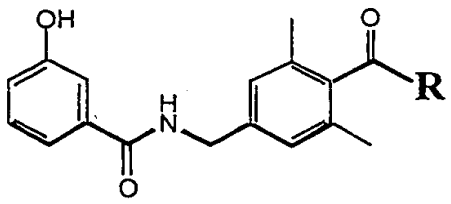
Example #	R group
277	thiophene 2- carboxylic acid
278	2- furoic acid
279	2- pyrazinecarboxylic acid
280	3- methyl thiophene 2- carboxylic acid
281	3- methyl 2- furoic acid
282	3- chloro thiophene 2- carboxylic acid

Example 283



Example 283 was synthesized by Method S55.

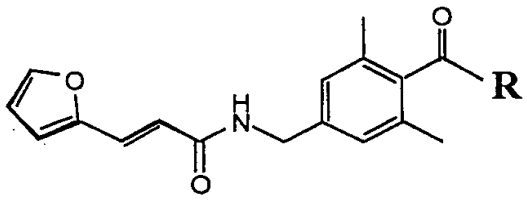
Examples 284-285



Examples 284-285 were synthesized by Method S56.

Example #	R group
284	L- Ala
285	L- Asn

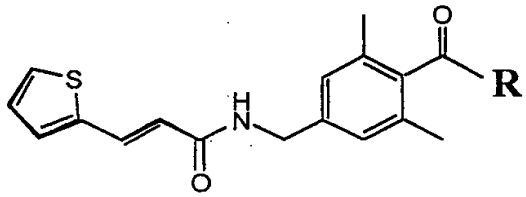
Examples 286-287



Examples 286-287 were synthesized by Method S57.

Example #	R group
286	L- diaminopropionic acid (alloc)
287	L- Lys

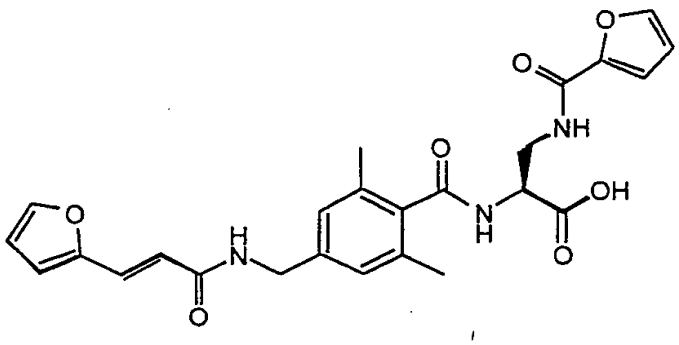
Examples 288-289



Examples 288-289 were synthesized by Method S58.

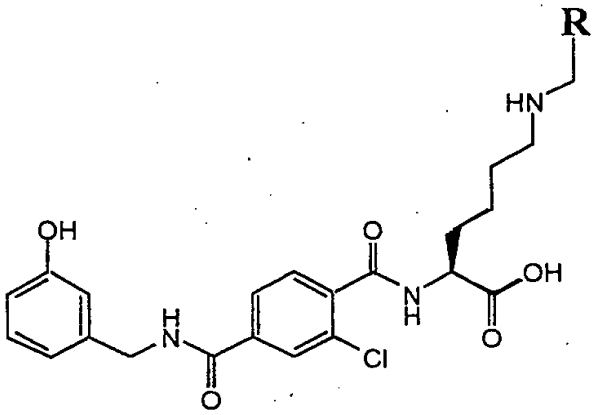
Example #	R group
288	L- diaminopropionic acid (alloc)
289	L- Lys

Example 290



Example 290 was synthesized by Method S59.

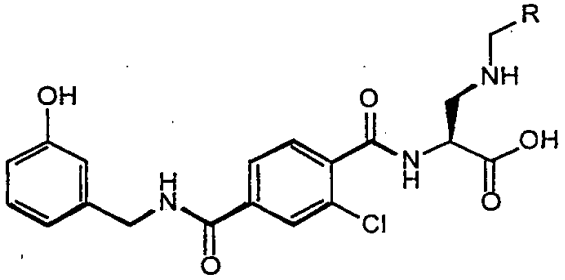
Examples 291-292



Examples 291-292 were synthesized by Method S60.

Example #	R group
291	2- furaldehyde
292	3- methyl 2- furaldehyde

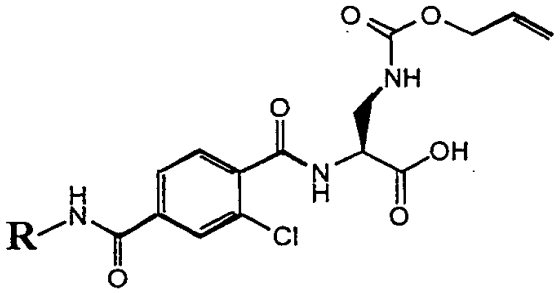
Examples 293-294



Examples 293-294 were synthesized by Method S61.

Example #	R group
293	2- furaldehyde
294	3- methyl 2- furaldehyde

Examples 295-296

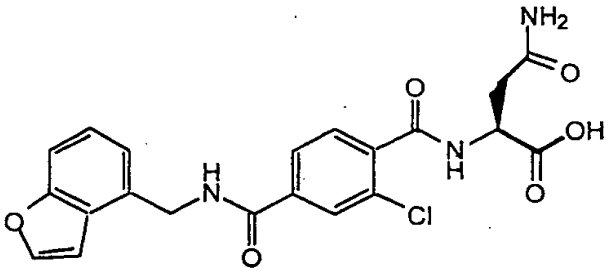


Examples 295-296 were synthesized by Method S62.

Example #	R group
295	6- aminomethyl benzofuran

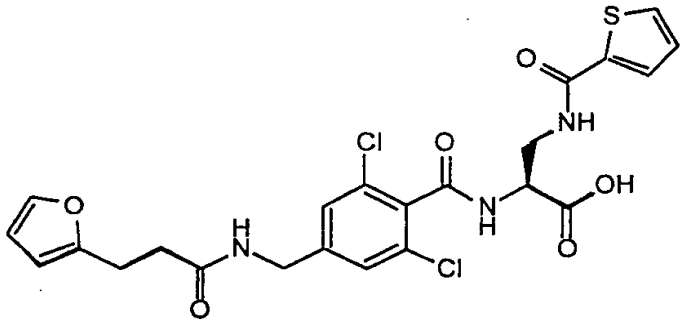
296 4- aminomethyl benzofuran

Example 297



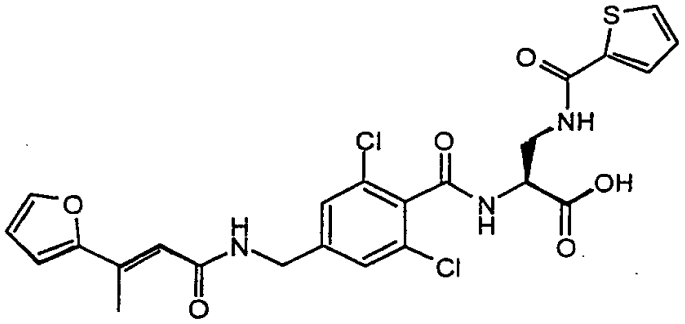
Example 297 was synthesized by Method S63.

Example 298



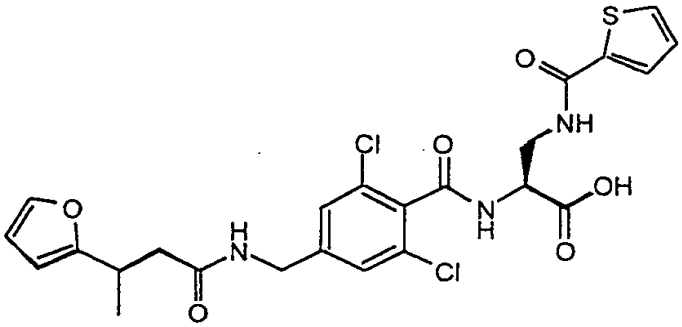
Example 298 was synthesized by Method S64.

Example 299



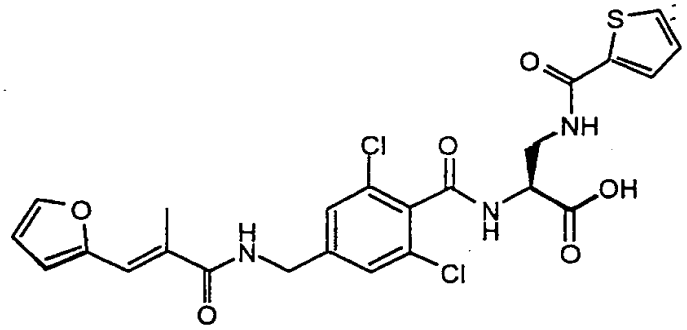
Example 299 was synthesized by Method S65.

Example 300



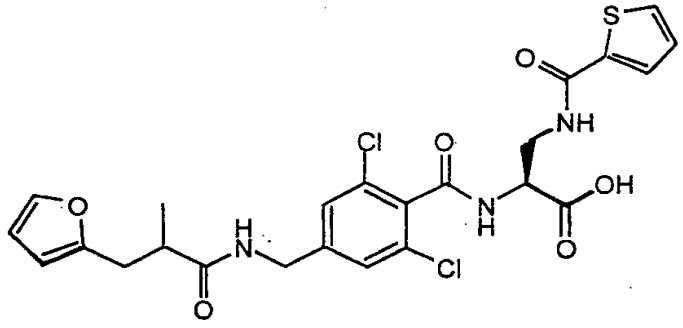
Example 300 was synthesized by Method S66.

Example 301



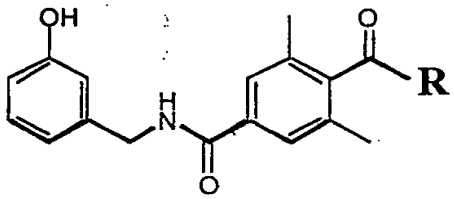
Example 301 was synthesized by Method S67.

Example 302



Example 302 was synthesized by Method S68.

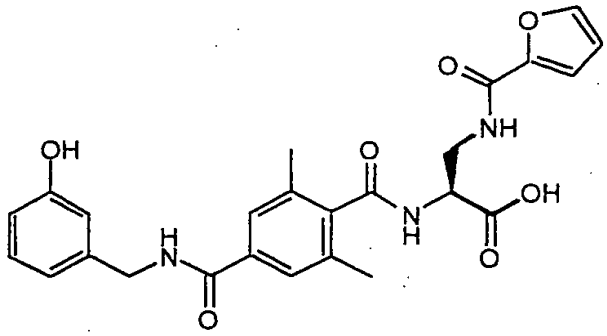
Examples 303-305



Examples 303-305 were synthesized by Method S69.

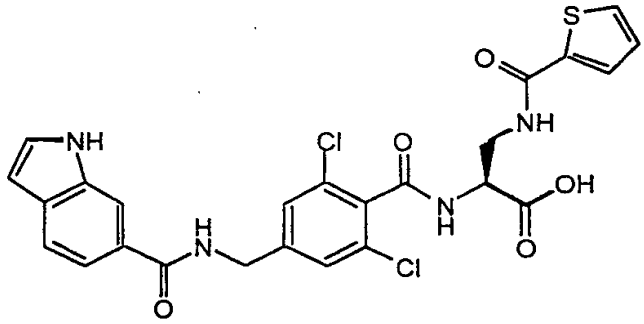
Example #	R group
303	L- Asn
304	L- diaminopropionic acid (alloc)
305	L- lys

Example 306



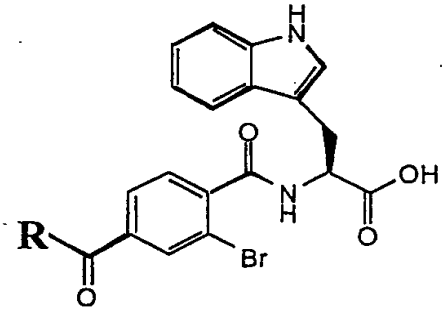
Example 306 was synthesized by Method S70.

Example 307



Example 307 was synthesized by Method S71.

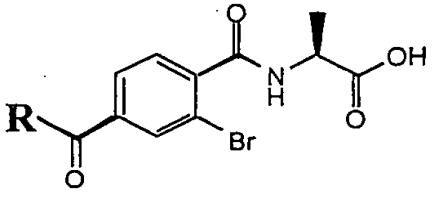
Examples 308-309



Examples 308-309 were synthesized by Method S72.

Example #	R group
308	3- hydroxy benzylamine
309	3-(3-hydroxyphenyl)propargylamine

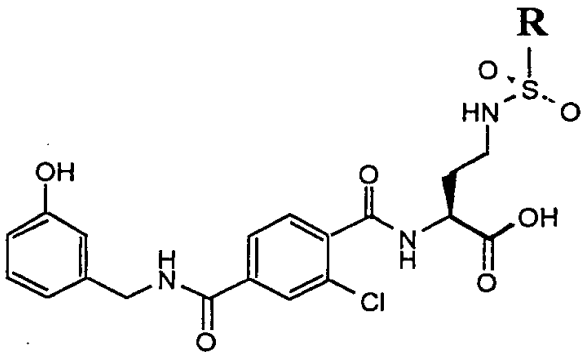
Examples 310-312



Examples 310-312 were synthesized by Method S73.

Example #	R group
310	3- flouro benzylamine
311	benzylamine
312	3-(3-hydroxyphenyl)propargylamine

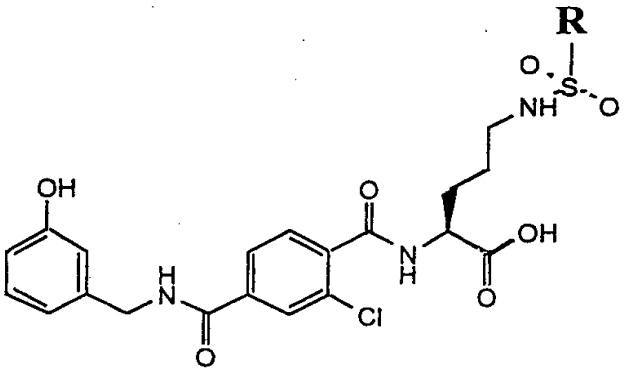
Examples 313-315



Examples 313-315 were synthesized by Method S74.

Example #	R group
313	N-acetylsulfanilyl chloride
314	2-bromobenzenesulfonyl chloride
315	2-thiophenesulfonyl chloride

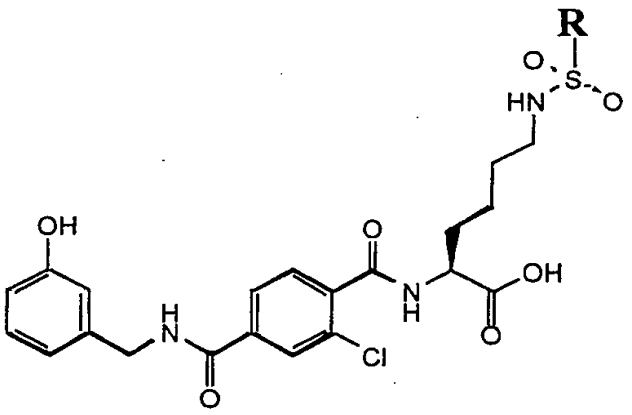
Examples 316-317



Examples 316-317 were synthesized by Method S75.

Example #	R group
316	2-thiophenesulfonyl chloride
317	8-quinolinesulfonyl chloride

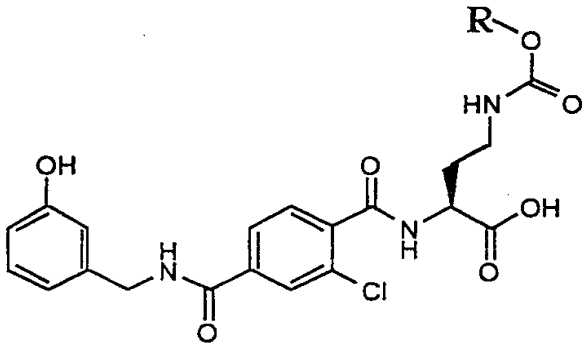
Examples 318-322



Examples 318-322 were synthesized by Method S76.

Example #	R group
318	benzenesulfonyl chloride
319	N-acetylsulfanilyl chloride
320	2-thiophenesulfonyl chloride
321	2-bromobenzenesulfonyl chloride
322	2-acetamido-4-methyl-5-thiazolesulfonyl chloride

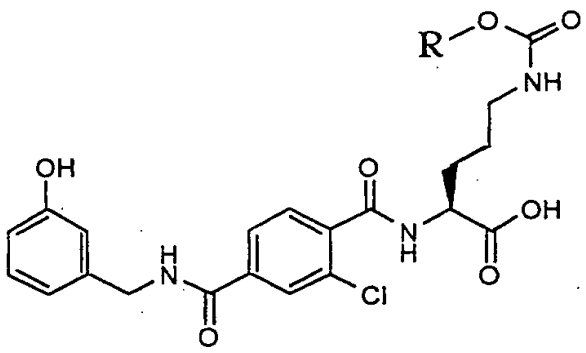
Examples 323-328



Examples 323-328 were synthesized by Method S77.

Example #	R group
323	isobutyl chloroformate
324	allyl chloroformate
325	butyl chloroformate
326	ethyl chloroformate
327	isopropyl chloroformate
328	propyl chloroformate

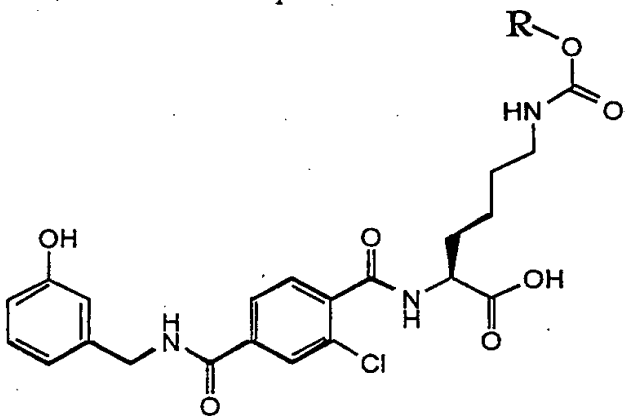
Examples 329-333



Examples 329-333 were synthesized by Method S78.

Example #	R group
329	isobutyl chloroformate
330	cyclopropyl chloroformate
331	ethyl chloroformate
332	methyl chloroformate
333	2, 2, 2-trichloroethyl chloroformate

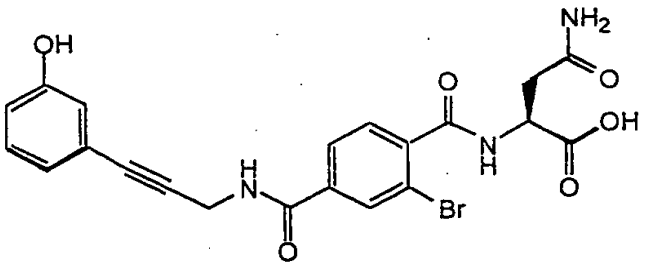
Examples 334-337



Examples 334-337 were synthesized by Method S79.

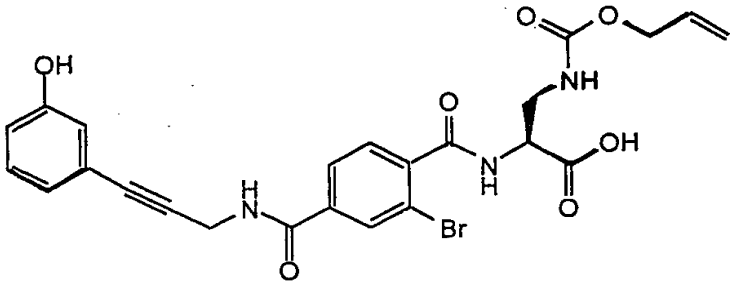
Example #	R group
334	butyl chloroformate
335	propyl chloroformate
336	ethyl chloroformate
337	methyl chloroformate

Example 338



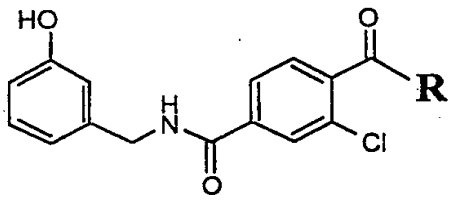
Example 338 was synthesized by Method S80.

Example 339



Example 339 was synthesized by Method S81.

Examples 340-354

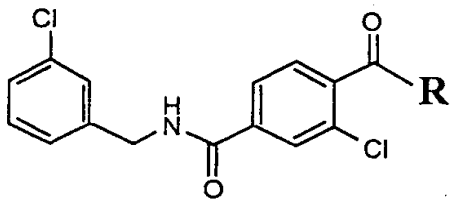


Examples 340-354 were synthesized by Method S82.

Example #	R group
340	L - Ala
341	L - Thr
342	L - Trp
343	L - aza Trp
344	L - Ser(OBzl)
345	L - Asn
346	L - Lys
347	L - His
348	L - Lys(N- e- Ac)
349	L - Gln
350	L-diaminopropionic(alloc) acid
351	L-diaminobutyric(alloc) acid
352	L-lys(alloc)
353	L-orn(alloc)

354 L-Tyr

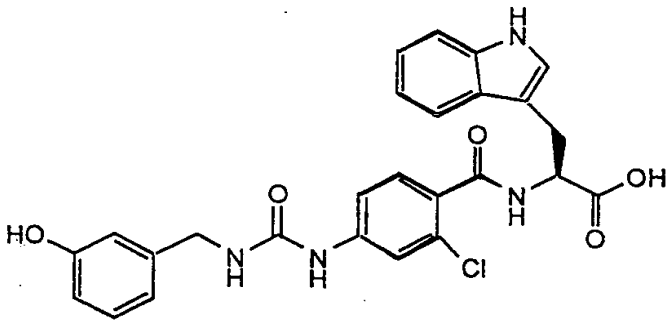
Examples 355-357



Examples 355-357 were synthesized by Method S83.

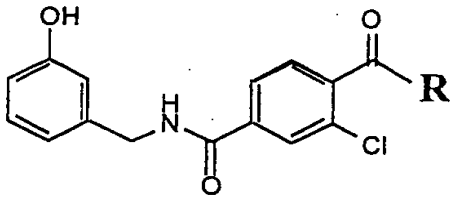
Example #	R group
355	L - Ala
356	L - His
357	L - Asn

Example 358



Example 358 was synthesized by Method S84.

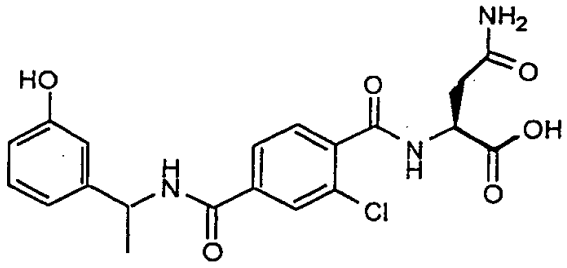
Examples 359-362



Examples 359-362 were synthesized by Method S85.

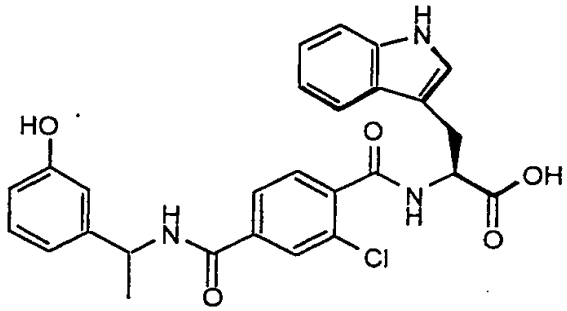
Example #	R group
359	1-amino-1-cyclopropane carboxylic acid
360	m-tyrosine
361	o-hydroxytyrosine
362	L-iodotyrosine

Example 363



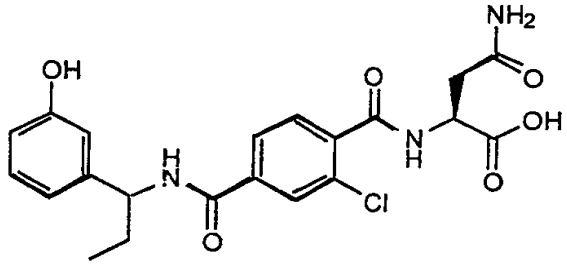
Example 363 was synthesized by Method S86.

Example 364



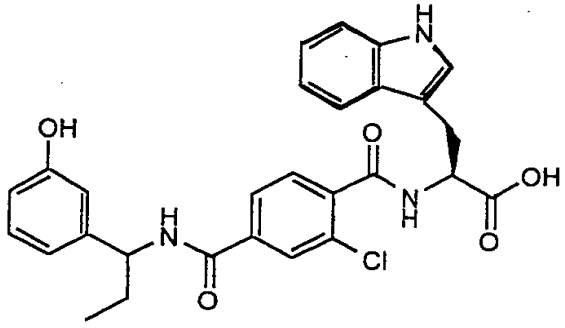
Example 364 was synthesized by Method S87.

Example 365



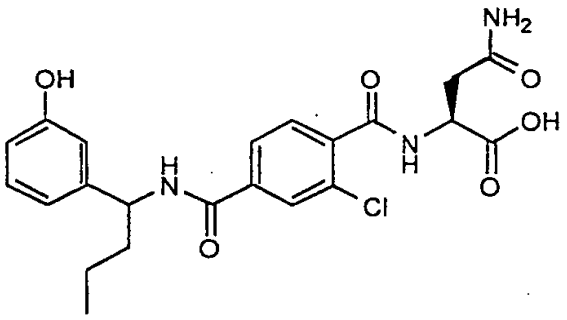
Example 365 was synthesized by Method S88.

Example 366



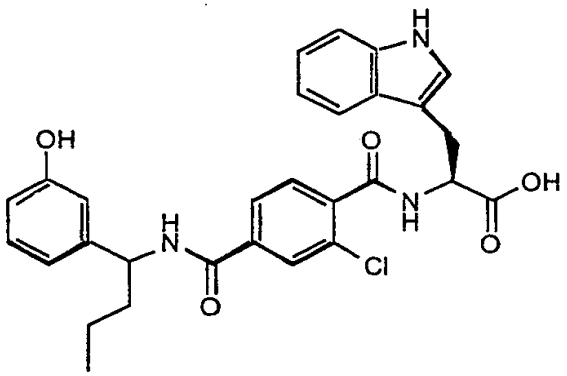
Example 366 was synthesized by Method S89.

Example 367



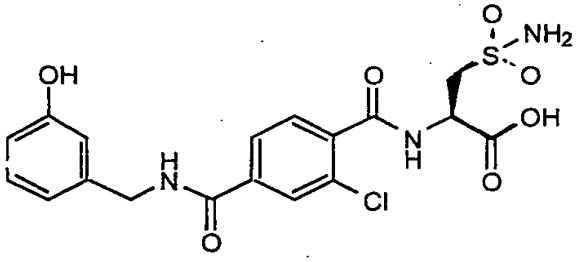
Example 367 was synthesized by Method S90.

Example 368



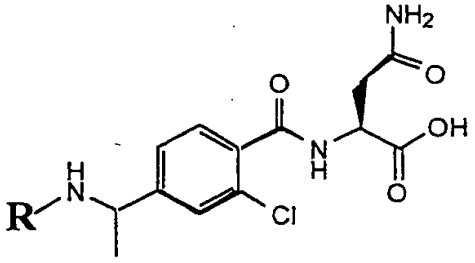
Example 368 was synthesized by Method S91.

Example 369



Example 369 was synthesized by Method S92.

Examples 370-371

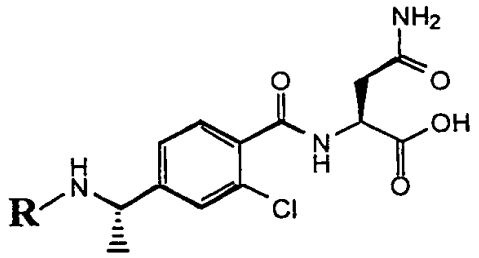


Examples 370-371 were synthesized by Method S93.

Example #	R group
370	3 - hydroxybenzoic acid

371		benzoic acid

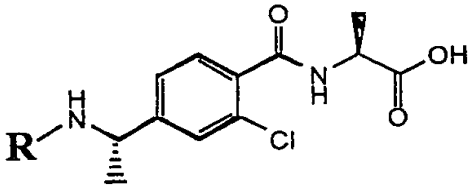
Examples 372-375



Examples 372-375 were synthesized by Method S94.

Example #	R group
372	furylacrylic acid
373	3-(2-thienyl)-acrylic acid
374	3 - hydroxybenzoic acid
375	benzoic acid

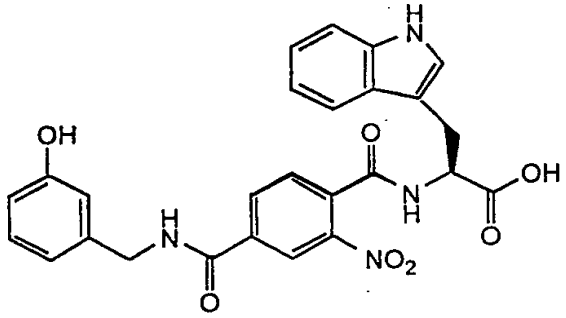
Examples 376-377



Examples 376-377 were synthesized by Method S95.

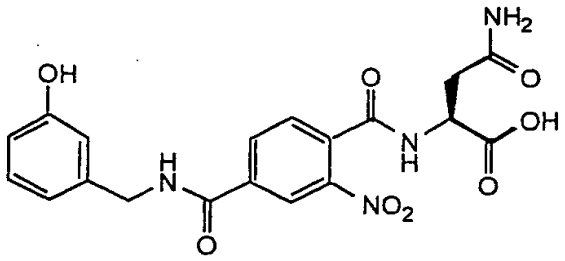
Example #	R group
376	3 - hydroxybenzoic acid
377	3-(2-thienyl)-acrylic acid

Example 378



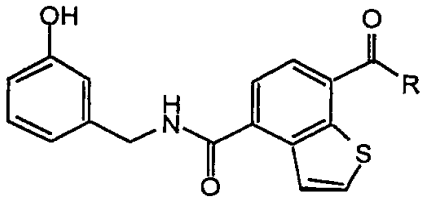
Example 378 was synthesized by Method S96.

Example 379



Example 379 was synthesized by Method S97.

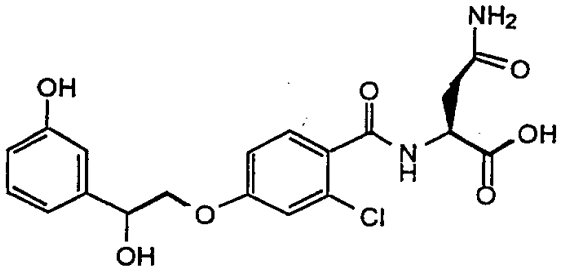
Examples 380-383



Examples 380-383 were synthesized by Method S98.

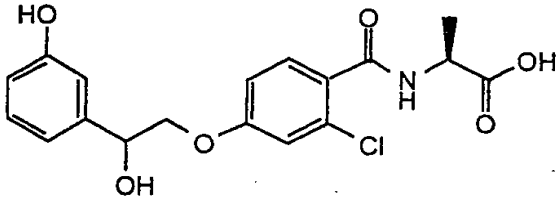
Example #	R group
380	L- Trp
381	L- Asn
382	L- dapa(alloc)
383	L- Lys

Example 384



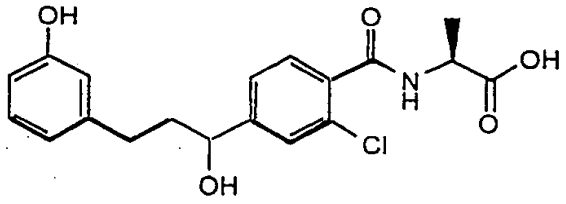
Example 383 was synthesized by Method S99.

Example 385



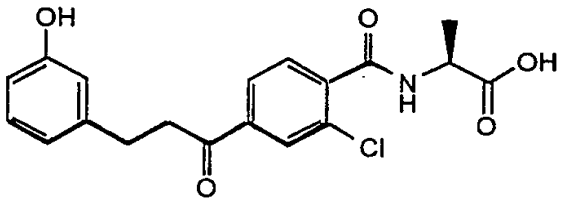
Example 385 was synthesized by Method S100.

Example 386



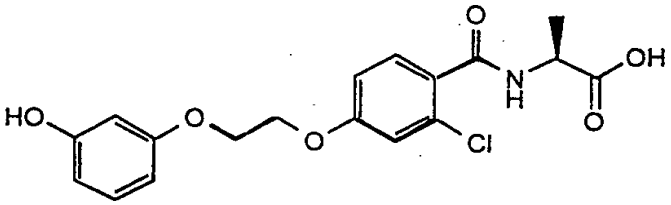
Example 386 was synthesized by Method S101.

Example 387



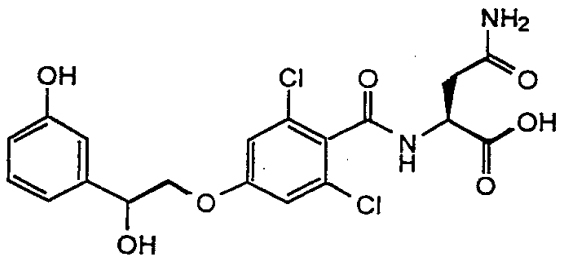
Example 387 was synthesized by Method S102.

Example 388



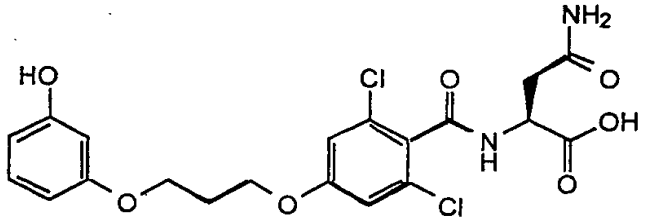
Example 388 was synthesized by Method S103.

Example 389



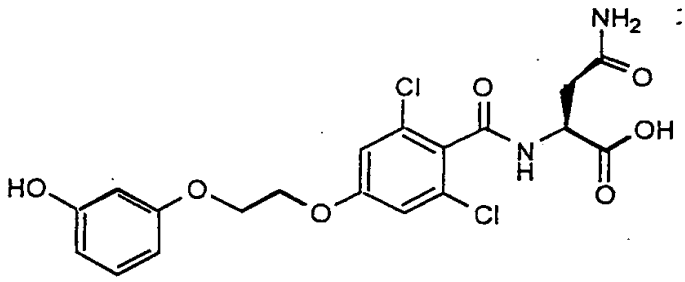
Example 389 was synthesized by Method S104.

Example 390



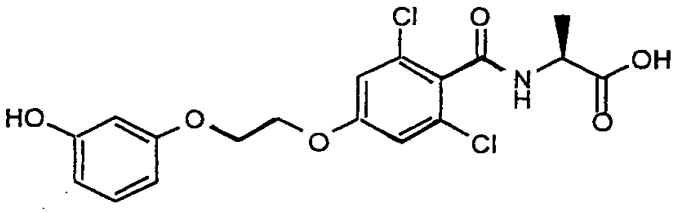
Example 390 was synthesized by Method S105.

Example 391



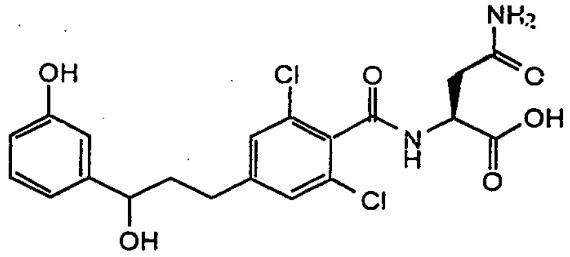
Example 391 was synthesized by Method S106.

Example 392



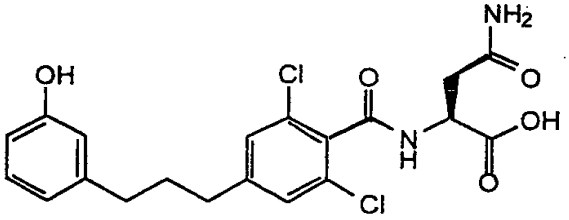
Example 392 was synthesized by Method S107.

Example 393



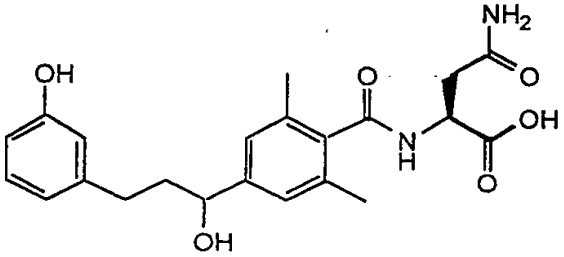
Example 393 was synthesized by Method S108.

Example 394



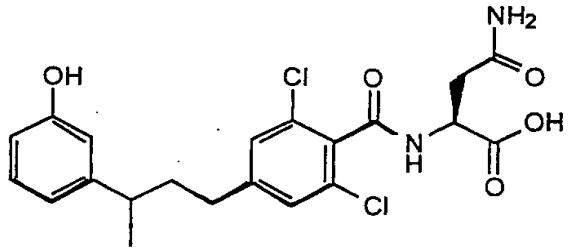
Example 394 was synthesized by Method S109.

Example 395



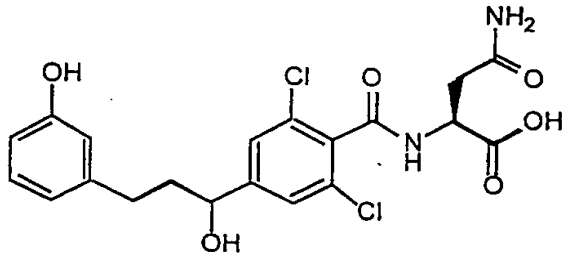
Example 395 was synthesized by Method S110.

Example 396



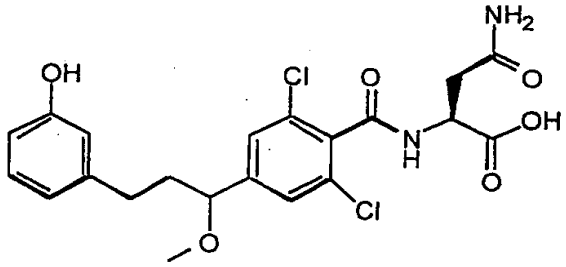
Example 396 was synthesized by Method S111.

Example 397



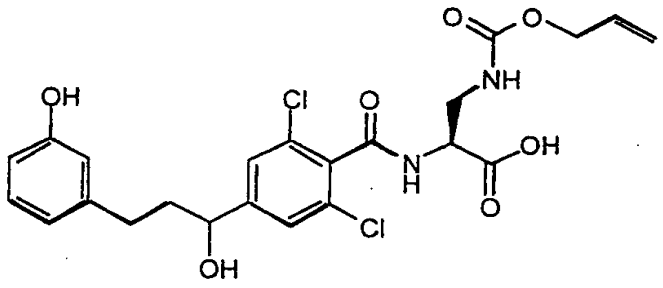
Example 397 was synthesized by Method S112.

Example 398



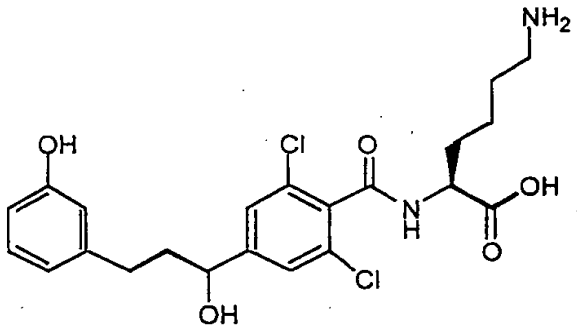
Example 398 was synthesized by Method S113.

Example 399



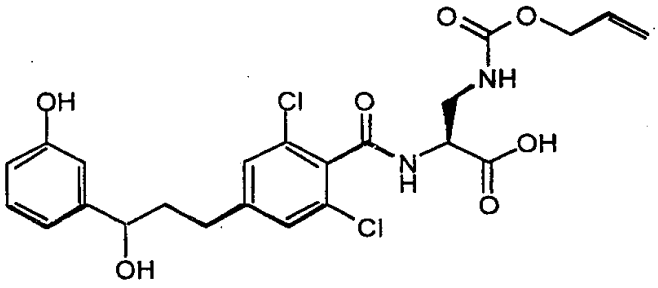
Example 399 was synthesized by Method S114.

Example 400



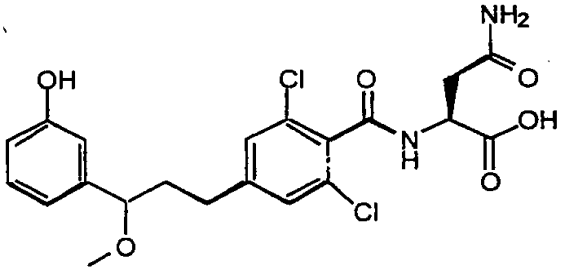
Example 400 was synthesized by Method S115.

Example 401



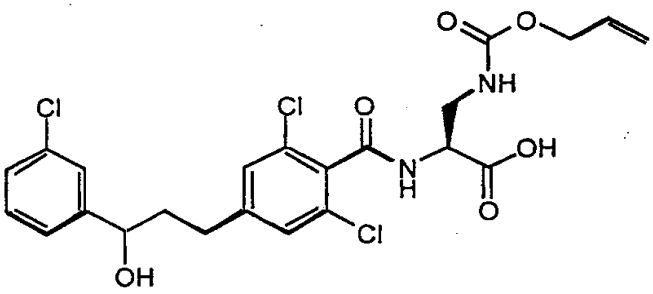
Example 401 was synthesized by Method S116.

Example 402



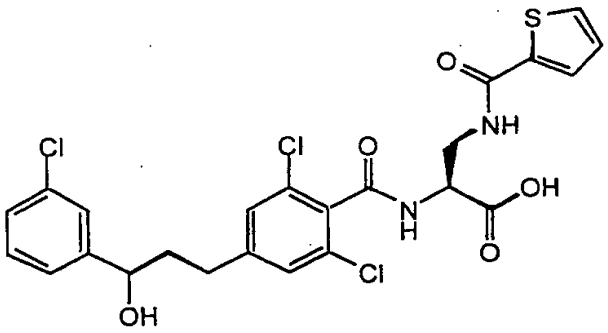
Example 402 was synthesized by Method S117.

Example 403



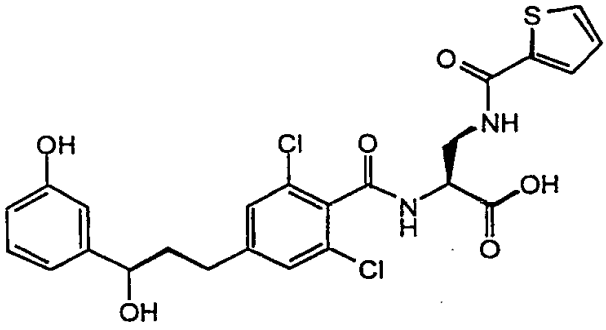
Example 403 was synthesized by Method S118.

Example 404



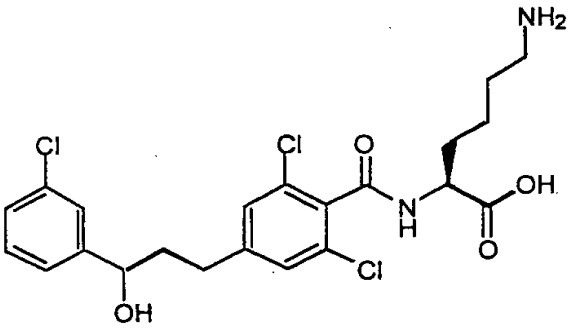
Example 404 was synthesized by Method S119.

Example 405



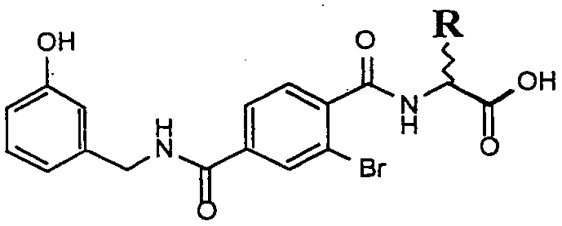
Example 405 was synthesized by Method S120.

Example 406



Example 406 was synthesized by Method S121.

Examples 407-416

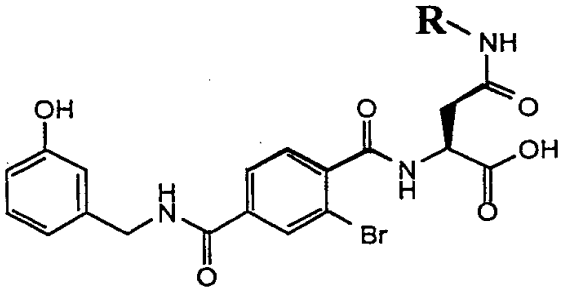


Examples 407-416 were synthesized by Method S122.

Example #	R group
407	3-methoxybenzyl bromide

408	3-bromobenzyl bromide
409	3, 5-dimethoxybenzyl bromide
410	5-bromovaleronitrile
411	6-bromochexanenitrile
412	3-nitrobenzyl bromide
413	3-cyanobenzyl bromide
414	5-bromomethyl-furan-2-carboxylic acid ethyl ester
415	5-bromomethyl-furan-2-carboxylic acid ethyl ester
416	3-bromomethyl benzamide

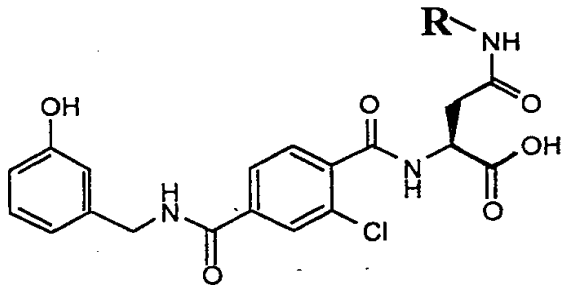
Examples 417-423



Examples 417-413 were synthesized by Method S123.

Example #	R group
417	1-aminonaphthalene
418	2-cyanoaniline
419	3-cyanoaniline
420	2-fluoroaniline
421	3-fluoroaniline
422	4-fluoroaniline
423	3-methoxyaniline

Examples 424-436

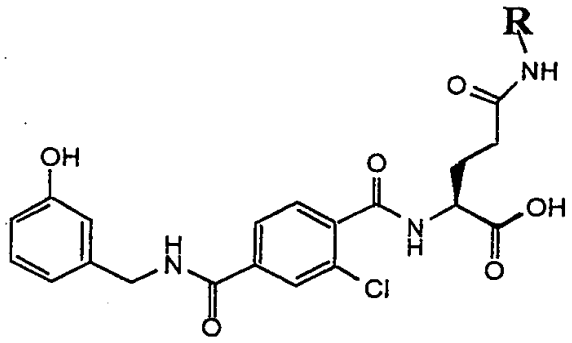


Examples 424-436 were synthesized by Method S124.

Example #	R group
424	2-(aminomethyl)pyridine
425	3-fluorobenzylamine

426	benzylamine
427	allylamine
428	phenethyl amine
429	histamine
430	4-fluorobenzylamine
431	3-methoxyphenethylamine
432	4-aminobenzylamine
433	2-aminobenzylamine
434	2-[1, 3]Dioxan-5-yl-ethylamine
435	piperonylamine
436	aniline

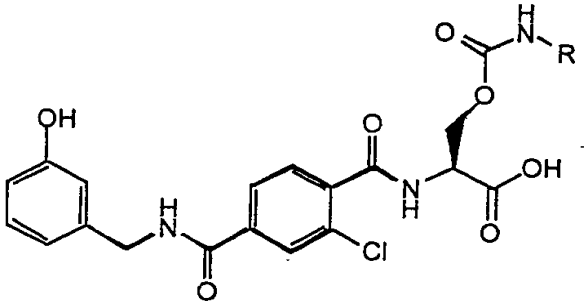
Examples 437-440



Examples 437-440 were synthesized by Method S125.

Example #	R group
437	isoamyl amine
438	4-(aminomethyl)pyridine
439	2-[1, 3]Dioxan-5-yl-ethylamine
440	aniline

Examples 441-443

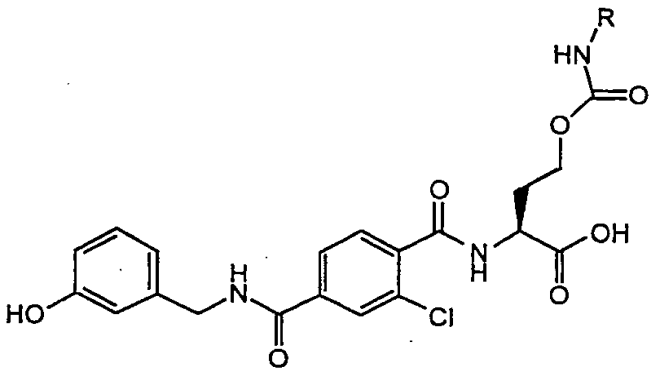


Examples 441-443 were synthesized by Method S126.

Example #	R group
441	o- toluidine
442	allyl amine

443	propyl amine	

Examples 444-459



Examples 444-459 were synthesized by Method S127.

Example #	R group
444	propylamine
445	3-(aminomethyl)pyridine
446	4-(aminomethyl)pyridine
447	2- methylbenzylamine
448	3- methylbenzylamine
449	4- methylbenzylamine
450	(S)-(-)-a-methylbenzylamine
451	2-(aminomethyl)pyridine
452	2- fluoro benzylamine
453	3- fluoro benzylamine
454	4- fluoro benzylamine
455	3- chloro benzylamine
456	4- chloro benzylamine
457	4- methoxy benzylamine
458	1- naphthalenemethylamine
459	benzylamine

Table 3 provides biological assay data for the compounds prepared by the methods described above. Data is provided for two assay formats: the forward format of LFA/ICAM assay (PPFF) and the PLM2 antibody capture format of LFA/ICAM assay (PLM2).

Table 3

PPFF and PLM2 assay data for exemplary compounds

Example #	PPFF(μM)	PLM2(μM)
1	0.149	0.028
2		0.035
3		0.069

	4	0.038
	5	0.013
	6	0.045
	7	0.004
5	8	0.021
	9	0.033
	10	0.003
	11	0.065
	12	0.029
10	13	0.064
	14	0.024
	15	0.010
	16	0.011
	17	0.036
15	18	0.010
	19	0.037
	20	0.029
	21	0.023
	22	0.019
20	23	0.072
	24	0.012
	25	0.019
	26	0.021
	27	0.008
25	28	0.092
	29	0.055
	30	0.064
	31	0.014
	32	0.047
30	33	0.023
	34	0.078
	35	0.069
	36	0.013
	37	0.038
35	38	0.013
	39	0.021
	40	0.076
	41	0.098

42	0.046
43	0.098
44	0.095
45	0.059
46	0.066
47	0.070
48	0.046
49	0.038
50	0.052
51	0.056
52	0.050
53	0.094
54	0.014
55	0.047
56	0.052
57	0.036
58	0.080
59	0.066
60	0.078
61	0.052
62	0.046
63	0.062
64	0.055
65	0.044
66	0.072
67	0.046
68	0.071
69	0.084
70	0.088
71	0.040
72	0.063
73	0.063
74	0.087
75	0.011
76	0.010
77	0.017
78	0.031
79	0.033

80	0.005
81	0.008
82	0.004
83	0.006
84	0.001
85	0.003
86	0.012
87	0.009
88	0.005
89	0.004
90	0.021
91	0.004
92	0.066
93	0.024
94	0.002
95	0.006
96	0.070
97	0.042
98	0.033
99	0.046
100	0.031
101	0.022
102	0.025
103	0.044
104	0.044
105	0.004
106	0.026
107	0.087
108	0.021
109	0.026
110	0.052
111	0.007
112	0.036
113	0.086
114	0.018
115	0.073
116	0.026
117	0.045

118	0.031
119	0.077
120	0.064
121	0.055
122	0.050
123	0.054
124	0.035
125	0.058
126	0.033
127	0.017
128	0.035
129	0.029
130	0.036
131	0.025
132	0.057
133	0.020
134	0.053
135	0.021
136	0.029
137	0.039
138	0.071
139	0.064
140	0.023
141	0.068
142	0.074
143	0.031
144	0.093
145	0.004
146	0.004
147	0.004
148	0.004
149	0.004
150	0.004
151	0.004
152	0.004
153	0.003
154	0.003
155	0.006

156	0.009
157	0.007
158	0.004
159	0.017
160	0.004
161	0.004
162	0.004
163	0.005
164	0.012
165	0.015
166	0.018
167	0.017
168	0.012
169	0.006
170	0.007
171	0.011
172	0.037
173	0.010
174	0.004
175	0.005
176	0.011
177	0.006
178	0.011
179	0.009
180	0.011
181	0.016
182	0.011
183	0.013
184	0.016
185	0.016
186	0.015
187	0.017
188	0.018
189	0.018
190	0.016
191	0.016
192	0.029
193	0.014

194	0.012
195	0.016
196	0.019
197	0.017
198	0.019
199	0.029
200	0.018
201	0.013
202	0.023
203	0.037
204	0.025
205	0.082
206	0.023
207	0.062
208	0.021
209	0.053
210	0.022
211	0.019
212	0.016
213	0.035
214	0.028
215	0.027
216	0.022
217	0.031
218	0.018
219	0.018
220	0.016
221	0.042
222	0.021
223	0.035
224	0.026
225	0.029
226	0.025
227	0.034
228	0.018
229	0.026
230	0.016
231	0.003

	232		0.005
	233		0.001
	234		0.044
	235		0.002
5	236		0.004
	237		0.003
	238	0.099	
	239	0.180	0.053
	240	0.085	
10	241	0.053	
	242	0.054	
	243	0.082	
	244	0.077	0.078
	245	0.058	0.164
15	246	0.067	0.059
	247	0.022	0.034
	248	0.027	0.026
	249	0.030	
	250		0.034
20	251		0.038
	252		0.060
	253		0.014
	254	0.094	0.036
	255	0.042	
25	256	0.076	
	257		0.042
	258		0.038
	259		0.049
	260		0.071
30	261		0.052
	262		0.075
	263		0.066
	264		0.093
	265		0.045
35	266		0.046
	267		0.021
	268		0.019
	269		0.046

	270		0.055
	271		0.086
	272		0.080
	273		0.016
5	274		0.006
	275		0.006
	276		0.012
	277		0.003
	278		0.002
10	279		0.004
	280		0.007
	281		0.004
	282		0.024
	283	0.092	
15	284	0.093	0.079
	285	0.064	
	286		0.014
	287		0.043
	288		0.023
20	289		0.074
	290		0.009
	291		0.007
	292		0.015
	293		0.083
25	294		0.100
	295		0.047
	296		0.017
	297		0.028
	298		0.009
30	299		0.016
	300		0.074
	301		0.025
	302		0.023
	303		0.005
35	304		0.003
	305		0.015
	306		0.004
	307		0.004

	308	0.061	
	309		0.057
	310	0.082	
	311	0.079	
5	312		0.089
	313		0.069
	314		0.028
	315		0.037
	316		0.030
10	317		0.055
	318		0.031
	319		0.023
	320		0.007
	321		0.020
15	322		0.011
	323		0.036
	324		0.042
	325		0.056
	326		0.042
20	327		0.070
	328		0.074
	329		0.033
	330		0.009
	331		0.027
25	332		0.057
	333		0.090
	334		0.072
	335		0.096
	336		0.066
30	337		0.079
	338		0.060
	339		0.020
	340	0.014	0.006
	341	0.031	
35	342	0.057	0.004
	343	0.030	
	344	0.183	0.053
	345	0.019	0.004

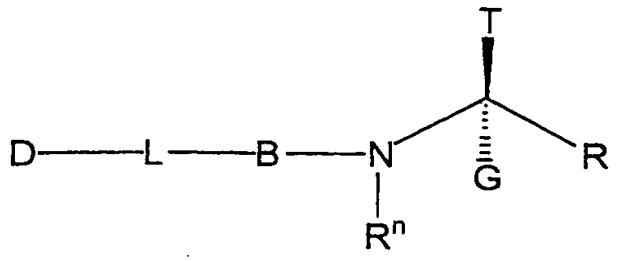
	346	0.071	
	347	0.044	0.004
	348	0.090	0.023
	349	0.042	
5	350	0.027	0.005
	351	0.067	0.032
	352		0.042
	353		0.074
	354		0.008
10	355	0.100	0.094
	356	0.068	
	357	0.057	0.023
	358	0.230	0.032
	359		0.016
15	360		0.018
	361		0.018
	362		0.005
	363	0.014	0.010
	364	0.087	0.035
20	365		0.024
	366		0.062
	367		0.020
	368		0.043
	369		0.019
25	370	0.055	0.025
	371	0.055	0.037
	372		0.013
	373		0.021
	374		0.021
30	375		0.040
	376	0.078	0.061
	377	0.016	0.051
	378		0.007
	379		0.010
35	380		0.096
	381		0.035
	382		0.012
	383		0.060

384	0.046	0.018
385	0.070	0.048
386	0.030	
387	0.098	0.043
388	0.050	
389	0.054	0.010
390		0.079
391		0.007
392		0.025
393		0.003
394		0.012
395		0.006
396		0.062
397		0.005
398		0.015
399		0.002
400		0.007
401		0.002
402		0.004
403		0.009
404		0.002
405		0.001
406		0.022
407		0.045
408		0.071
409		0.054
410		0.065
411		0.055
412		0.074
413	0.051	0.045
414		0.087
415		0.059
416		0.036
417		0.086
418		0.056
419		0.079
420		0.015
421		0.056

	422		0.083
	423		0.032
	424		0.038
	425		0.082
5	426		0.057
	427		0.044
	428		0.029
	429		0.094
	430		0.070
10	431		0.070
	432		0.070
	433		0.046
	434		0.050
	435		0.074
15	436		0.011
	437	0.083	0.034
	438		0.082
	439		0.089
	440		0.068
20	441		0.015
	442		0.006
	443		0.010
	444		0.041
	445		0.029
25	446		0.020
	447		0.085
	448		0.094
	449		0.071
	450		0.061
30	451		0.030
	452		0.040
	453		0.056
	454		0.046
	455		0.071
35	456		0.064
	457		0.036
	458		0.083
	459		0.058

WHAT IS CLAIMED IS:

1) A method of treating or ameliorating an immune or inflammatory response or disorder in a mammal mediated through the CD11/CD18 family of cellular adhesion molecules comprising administrating to the mammal a therapeutically effective amount of a compound represented by structural formula (I)



(I)

where

D is a mono-, bi-, or tricyclic saturated, unsaturated, or aromatic ring, each ring having 5-, 6- or 7 atoms in the ring where the atoms in the ring are carbon or from one to four heteroatoms selected from the group nitrogen, oxygen, and sulfur, where any carbon or sulfur ring atom may optionally be oxidized, each ring substituted with 0-3 R^d;

L is a bivalent linking group selected from the group

$-L^3-L^2-L^1-$,

$-L^4-L^3-L^2-L^1-$ and

$-L^5-L^4-L^3-L^2-L^1-$,

where

L^1 is selected from oxo (-O-), $S(O)_s$, C(=O), $CR^1R^{1'}$, CR^1, het, NR^n and N,

L^2 is selected from oxo (-O-), $S(O)_s$, C(=O), C(=N-O-R^o), $CR^2R^{2'}$, CR^2, het, NR^n and N,

L^3 is selected from oxo (-O-), $S(O)_s$, C(=O), C(=N-O-R^o), $CR^3R^{3'}$, CR^3, het, NR^n and N,

L^4 is absent or is selected from oxo (-O-), $S(O)_s$, C(=O), C(=N-O-R^o), $CR^4R^{4'}$, CR^4, NR^n and N, and

L^5 is absent or is selected from oxo (-O-), $S(O)_s$, C(=O), $CR^5R^{5'}$, CR^5, NR^n and N, provided that only one of L^1 - L^3 may be het and that when one of L^1 - L^3 is het the other L^1 - L^5 may be absent, where

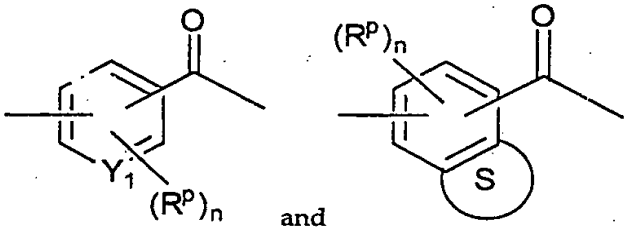
R^1, $R^{1'}$, R^2, $R^{2'}$, R^3, $R^{3'}$, R^4, $R^{4'}$, R^5 and $R^{5'}$ each are independently selected from R^a, R^c and U-Q-V-W,

optionally, R^2 and $R^{2'}$ separately or together may form a saturated, unsaturated or aromatic fused ring with B through a substituent R^p on B, the fused ring containing 5, 6 or 7 atoms in the ring and optionally containing 1-3 heteroatoms selected from the group O, S and N, where any S or N may optionally be oxadized;

optionally, R^3 and $R^{3'}$ separately or together and R^4 and $R^{4'}$ separately or together may form a saturated, unsaturated or aromatic fused ring with D through a substituent R^d on D, the fused ring containing 5, 6 or 7 atoms in the ring and optionally containing 1-3 heteroatoms selected from the group O, S and N, where any S or N may optionally be oxidized;

also optionally, each R^1-$R^{5'}$, NR^n or N in L^1- L^5 together with any other R^1- $R^{5'}$, NR^n or N in L^1-L^5 may form a 5, 6 or 7 member homo- or heterocycle either saturated, unsaturated or aromatic optionally containing 1-3 additional heteroatoms selected from N, O and S, where any carbon or sulfur ring atom may optionally be oxidized, each cycle substituted with 0-3 R^d; and where s is 0-2;

B is selected from the group



and

where

is a fused hetero- or homocyclic ring containing 5, 6 or 7 atoms, the ring being unsaturated, partially saturated or aromatic, the heteroatoms selected from 1-3 O, S and N,

Y_1 is selected from CH and NR^n;

n is 0-3:

G is selected from hydrogen and C_1-C_6alkyl, optionally G taken together with T may form a C_3-C_6cycloalkyl optionally substituted with -V-W;

T is selected from the group

a naturally occurring α-amino-acid side chain,

and U-Q-V-W;

U is an optionally substituted bivalent radical selected from the group

C_1-C_6alkyl,

C_0-C_6alkyl-Q,

C_2-C_6alkenyl-Q, and

C_2-C_6alkynyl-Q:

where the substituents on any alkyl, alkenyl or alkynyl are 1-3 R^a;

Q is absent or is selected from the group

-O-,

-$S(O)_s$-,

-SO_2-$N(R^n)$-,

-$N(R^n)$-,

-$N(R^n)$-C(=O)-,

-$N(R^n)$-C(=O)-$N(R^n)$-,

-$N(R^n)$-C(=O)-O-,

-$N(R^n)$-SO_2-,

-C(=O)-,

-C(=O)-O-,

-het-,

-C(=O)-$N(R^n)$-,

-O-C(=O)-$N(R^n)$-,

-$PO(OR^c)O$- and

-P(O)O-;

where

s is 0-2 and

het is a mono- or bicyclic 5, 6, 7, 9 or 10 member heterocyclic ring, each ring containing 1-4 heteroatoms selected from N, O and S, where the heterocyclic ring may be saturated, partially saturated, or aromatic and any N or S being optionally oxidized, the heterocyclic ring being substituted with 0-3 R^h;

V is absent or is an optionally substituted bivalent group selected from

C_1-C_6alkyl,

C_3-C_8cycloalkyl,

C_0-C_6alkyl-C_6-C_{10}aryl, and

C_0-C_6alky-het;

where the substituents on any alkyl are 1-3 R^a and the substituents on any aryl or het are 1-3 R^d;

W is selected from the group

hydrogen,

OR^o,

SR^m,

$NR^nR^{n'}$,

NH-C(=O)-O-R^c,

NH-C(=O)-$NR^nR^{n'}$,

NH-C(=O)-R^c,

NH-SO_2-R^s,

NH-SO_2-$NR^nR^{n'}$,

NH-SO_2-NH-C(=O)-R^c,

NH-C(=O)-NH-SO_2-R^s,

C(=O)-NH-C(=O)-O-R^c,

C(=O)-NH-C(=O)-R^c,

C(=O)-NH-C(=O)-$NR^nR^{n'}$,

C(=O)-NH-SO_2-R^s,

C(=O)-NH-SO_2-$NR^nR^{n'}$,

C(=S)-$NR^nR^{n'}$,

SO_2-R^s,

SO_2-O-R^s,

SO_2-$NR^nR^{n'}$,

SO_2-NH-C(=O)-O-R^c,

SO_2-NH-C(=O)-$NR^nR^{n'}$,

SO_2-NH-C(=O)-R^c,

O-C(=O)-$NR^nR^{n'}$,

O-C(=O)-R^c,

O-C(=O)-NH-C(=O)-R^c,

O-C(=O)-NH-SO_2-R^s and

O-SO_2-R^s;

R is selected from

C(=O)-R^z,

C(=O)-H,

CH_2(OH) and

CH_2O-C(=O)-C_1-C_6alkyl;

R^a is $R^{a'}$ or $R^{a''}$ subsitiuted with 1-3 $R^{a'}$; where

$R^{a'}$ is selected from the group

hydrogen,

halo(F. Cl, Br, I),

cyano,

isocyanate,

carboxy,

carboxy-C_1-C_{11}alkyl,

amino,

amino-C_1-C_8alkyl,

aminocarbonyl,

carboxamido,

carbamoyl,

carbamoyloxy,

formyl,

formyloxy,

azido,

nitro,

imidazoyl,

ureido,

thioureido,

thiocyanato,
hydroxy,
C_1-C_6alkoxy,
mercapto,
sulfonamido,
het,
phenoxy,
phenyl,
benzamido,
tosyl,
morpholino,
morpholinyl,
piperazinyl,
piperidinyl,
pyrrolinyl.
imidazolyl and
indolyl;

$R^{a''}$ is selected from the group
C_0-C_{10}alkyl-Q-C_0-C_6alkyl,
C_0-C_{10}alkenyl-Q-C_0-C_6alkyl,
C_0-C_{10}alkynyl-Q-C_0-C_6alkyl,
C_3-C_{11}cycloalkyl-Q-C_0-C_6alkyl,
C_3-C_{10}cycloalkenyl-Q-C_0-C_6alkyl,
C_1-C_6alkyl-C_6-C_{12}aryl-Q-C_0-C_6alkyl,
C_6-C_{10}aryl-C_1-C_6alkyl-Q-C_0-C_6alkyl,
C_0-C_6alkyl-het-Q-C_0-C_6alkyl,
C_0-C_6alkyl-Q-het-C_0-C_6alkyl,
het-C_0-C_6alkyl-Q-C_0-C_6alkyl,
C_0-C_6alkyl-Q-C_6-C_{12}aryl and
-Q-C_1-C_6alky;

R^c is selected from hydrogen and substituted or unsubstituted
C_1-C_{10}alkyl,

C_2-C_{10}alkenyl,

C_2-C_{10}alkynyl,

C_3-C_{11}cycloalkyl,

C_3-C_{10}cycloalkenyl,

C_1-C_6alkyl-C_6-C_{12}aryl,

C_6-C_{10}aryl-C_1-C_6alkyl,

C_1-C_6alkyl-het,

het-C_1-C_6alkyl,

C_6-C_{12}aryl and

het,

where the substituents on any alkyl, alkenyl or alkynyl are 1-3 R^a and the substituents on any aryl or het are 1-3 R^d;

R^d is selected from R^p and R^h;

R^h is selected from the group

OH,

OCF_3,

OR^c,

SR^m,

halo(F, Cl. Br, I),

CN,

isocyanate,

NO_2,

CF_3,

C_0-C_6alkyl-$NR^nR^{n'}$,

C_0-C_6alkyl-C(=O)-$NR^nR^{n'}$,

C_0-C_6alkyl-C(=O)-R^a,

C_1-C_8alkyl,

C_1-C_8alkoxy,

C_2-C_8alkenyl,

C_2-C_8alkynyl,

C_3-C_6cycloalkyl,

C_3-C_6cycloalkenyl,

C_1-C_6alkyl-phenyl,

phenyl-C_1-C_6alkyl,

C_1-C_6alkyloxycarbonyl,

phenyl-C_0-C_6alkyloxy,

C_1-C_6alkyl-het,

het-C_1-C_6alkyl,

SO_2-het,

-O-C_6-C_{12}aryl,

-SO_2-C_6-C_{12}aryl,

-SO_2-C_1-C_6alkyl and

het,

where any alkyl, alkenyl or alkynyl may optionally be substituted with 1-3 groups selected from OH, halo(F, Cl, Br, I), nitro, amino and aminocarbonyl and the substituents on any aryl or het are 1-2 hydroxy, halo(F, Cl, Br, I), CF_3, C_1-C_6alkyl, C_1-C_6alkoxy, nitro and amino;

R^m is selected from

S-C_1-C_6alkyl,

C(=O)-C_1-C_6alkyl,

C(=O)-$NR^nR^{n'}$,

C_1-C_6alkyl,

halo(F, Cl, Br, I)-C_1-C_6alkyl,

benzyl and

phenyl;

R^n is selected from the group

R^c,

NH-C(=O)-O-R^c,

NH-C(=O)-R^C,

NH-C(=O)-NHR^C,

NH-SO_2-R^S,

NH-SO_2-NH-C(=O)-R^C,

NH-C(=O)-NH-SO_2-R^S,

C(=O)-O-R^C,

C(=O)-R^C,

C(=O)-NHR^C,

C(=O)-NH-C(=O)-O-R^C,

C(=O)-NH-C(=O)-R^C,

C(=O)-NH-SO_2-R^S,

C(=O)-NH-SO_2-NHR^S,

SO_2-R^S,

SO_2-O-R^S,

SO_2-N(R^C)$_2$,

SO_2-NH-C(=O)-O-R^C,

SO_2-NH-C(=O)-O-R^C and

SO_2-NH-C(=O)-R^C;

$R^{n'}$ is selected from hydrogen, hydroxy and substituted or unsubstituted

C_1-C_{11}alkyl,

C_1-C_{11}alkoxy,

C_2-C_{10}alkenyl,

C_2-C_{10}alkynyl,

C_3-C_{11}cycloalkyl,

C_3-C_{10}cycloalkenyl,

C_1-C_6alkyl-C_6-C_{12}aryl,

C_6-C_{10}aryl-C_1-C_6alkyl,

C_6-C_{10}aryl-C_0-C_6alkyloxy,

C_1-C_6alkyl-het,

het-C_1-C_6alkyl,

C_6-C_{12}aryl,

het,

C_1-C_6alkylcarbonyl,

C_1-C_8alkoxycarbonyl,

C_3-C_8cycloalkylcarbonyl,

C_3-C_8cycloalkoxycarbonyl,

C_6-C_{11}aryloxycarbonyl,

C_7-C_{11}arylalkoxycarbonyl,

heteroarylalkoxycarbonyl,

heteroarylalkylcarbonyl,

heteroarylcarbonyl,

heteroarylalkylsulfonyl,

heteroarylsulfonyl,

C_1-C_6alkylsulfonyl and

C_6-C_{10}arylsulfonyl,

where the substituents on any alkyl, alkenyl or alkynyl are 1-3 R^a and the substituents on any aryl, het or heteroaryl are 1-3 R^d;

R^n and $R^{n'}$ taken together with the common nitrogen to which they are attached may from an optionally substituted heterocycle selected from

morpholinyl,

piperazinyl,

thiamorpholinyl,

pyrrolidinyl,

imidazolidinyl,

indolinyl,

isoindolinyl,

1,2,3,4-tetrahydro-quinolinyl,

1,2,3,4-tetrahydro-isoquinolinyl,
thiazolidinyl and
azabicyclononyl,

where the substituents are 1-3 R^a;

R^o is selected from hydrogen and substituted or unsubstituted
C_1-C_6alkyl,
C_1-C_6alkylcarbonyl,
C_2-C_6alkenyl,
C_2-C_6alkynyl,
C_3-C_8cycloalkyl and
benzoyl,

where the substituents on any alkyl are 1-3 R^a and the substituents on any aryl are 1-3 R^p;

R^p is selected from the group
OH,
halo(F, Cl. Br, I),
CN,
isocyanate,
OR^c,
SR^m,
SOR^c,
NO_2,
CF_3,
R^c,
$NR^nR^{n'}$,
$NR^n C(=O)-O-R^c$,
$NR^n C(=O)-R^c$,
C_0-C_6alkyl-SO_2-R^c,
C_0-C_6alkyl-SO_2-$NR^nR^{n'}$,
$C(=O)-R^c$,

O-C(=O)-R^c,

C(=O)-O-R^c and

C(=O)-$NR^nR^{n'}$,

where the substituents on any alkyl, alkenyl or alkynyl are 1-3 R^a and the substituents on any aryl or het are 1-3 R^d;

R^s is a substituted or unsubstituted group selected from

C_1-C_8alkyl,

C_2-C_8alkenyl,

C_2-C_8alkynyl,

C_3-C_8cycloalkyl,

C_3-C_6cycloalkenyl,

C_0-C_6alkyl-phenyl,

phenyl-C_0-C_6alkyl,

C_0-C_6alkyl-het and

het-C_0-C_6alkyl,

where the substituents on any alkyl, alkenyl or alkynyl are 1-3 R^a and the substituents on any aryl or het are 1-3 R^d;

R^z is a substituted or unsubstituted group selected from

hydroxy,

C_1-C_{11}alkoxy,

C_3-C_{12}cycloalkoxy,

C_8-C_{12}aralkoxy,

C_8-C_{12}arcycloalkoxy,

C_6-C_{10}aryloxy,

C_3-C_{10}alkylcarbonyloxyalkyloxy,

C_3-C_{10}alkoxycarbonyloxyalkyloxy,

C_3-C_{10}alkoxycarbonylalkyloxy,

C_5-C_{10}cycloalkylcarbonyloxyalkyloxy,

C_5-C_{10}cycloalkoxycarbonyloxyalkyloxy,

C_5-C_{10}cycloalkoxycarbonylalkyloxy,

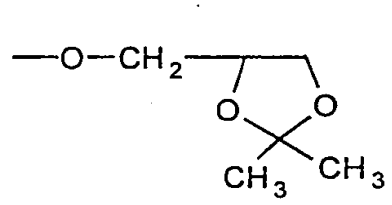
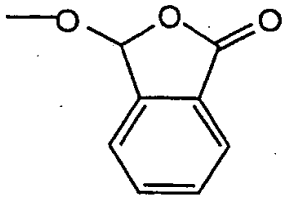
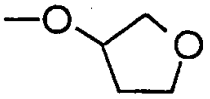
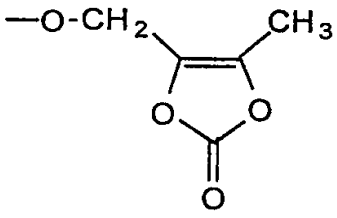
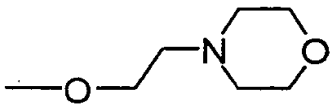
C_8-C_{12}aryloxycarbonylalkyloxy,

C_8-C_{12}aryloxycarbonyloxyalkyloxy,

C_8-C_{12}arylcarbonyloxyalkyloxy,

C_5-C_{10}alkoxyalkylcarbonyloxyalkyloxy,

$(R^n)(R^{n'})N(C_1$-C_{10}alkoxy)-,

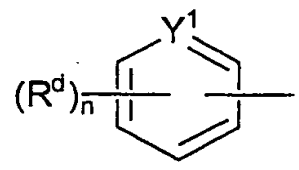
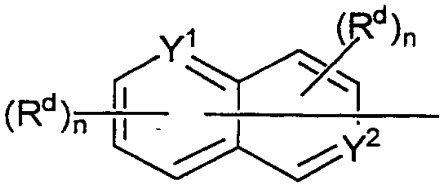
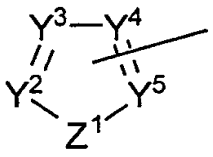
and

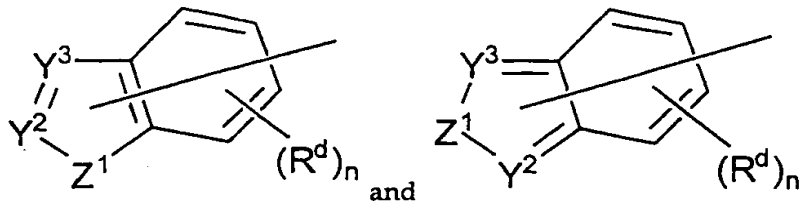
where the substituents on any alkyl, alkenyl or alkynyl are 1-3 R^a and the substituents on any aryl or het are 1-3 $R^{d'}$ and

pharmaceutically acceptable salts thereof.

2) The method of Claim 1 wherein

D is an aromatic homocycle or aromatic heterocycle containing 1-3 heteroatoms selected from the group N, S and O, the homo- or heterocycles selected from the group



where

Y^1, Y^2, Y^3, Y^4 and Y^5 are selected from the group CH, CR^d and N,

Z^1 is selected from the group O, S, N and NR^n,

n is 0-3,

R^d is selected from the group

OH, OCF_3, OR^c, SR^m, halo(F, Cl. Br, I), CN, isocyanate, NO_2, CF_3, C_0-C_6alkyl-$NR^nR^{n'}$, C_0-C_6alkyl-C(=O)-$NR^nR^{n'}$, C_0-C_6alkyl-C(=O)-R^a, C_1-C_8alkyl, C_1-C_8alkoxy, C_2-C_8alkenyl, C_2-C_8alkynyl, C_3-C_6cycloalkyl, C_3-C_6cycloalkenyl, C_1-C_6alkyl-phenyl, phenyl-C_1-C_6alkyl, C_1-C_6alkyloxycarbonyl, phenyl-C_0-C_6alkyloxy, C_1-C_6alkyl-het, het-C_1-C_6alkyl, SO_2-het, -O-C_6-C_{12}aryl, -SO_2-C_6-C_{12}aryl, -SO_2-C_1-C_6alkyl and het, where any alkyl, alkenyl or alkynyl may optionally be substituted with 1-3 groups selected from OH, halo(F, Cl, Br, I), nitro, amino and aminocarbonyl and the substituents on any aryl or het are 1-2 hydroxy, halo(F, Cl, Br, I), CF_3, C_1-C_6alkyl, C_1-C_6alkoxy, nitro and amino;

R^a is $R^{a'}$ or $R^{a''}$ subsitiuted with 1-3 $R^{a'}$; where

$R^{a'}$ is selected from the group

hydrogen, halo(F. Cl, Br, I), cyano, isocyanate, carboxy, carboxy-C_1-C_{11}alkyl, amino, amino-C_1-C_8alkyl, aminocarbonyl, carboxamido, carbamoyl, carbamoyloxy, formyl, formyloxy, azido, nitro, imidazoyl, ureido, thioureido, thiocyanato, hydroxy, C_1-C_6alkoxy, mercapto, sulfonamido, het, phenoxy, phenyl, benzamido, tosyl, morpholino, morpholinyl, piperazinyl, piperidinyl, pyrrolinyl. imidazolyl and indolyl;

$R^{a''}$ is selected from the group

C_0-C_{10}alkyl-Q-C_0-C_6alkyl, C_0-C_{10}alkenyl-Q-C_0-C_6alkyl, C_0-C_{10}alkynyl-Q-C_0-C_6alkyl, C_3-C_{11}cycloalkyl-Q-C_0-C_6alkyl, C_3-C_{10}cycloalkenyl-Q-C_0-C_6alkyl, C_1-C_6alkyl-C_6-C_{12}aryl-Q-C_0-C_6alkyl, C_6-C_{10}aryl-C_1-C_6alkyl-Q-C_0-C_6alkyl, C_0-C_6alkyl-het-Q-C_0-

C_6alkyl, C_0-C_6alkyl-Q-het-C_0-C_6alkyl, het-C_0-C_6alkyl-Q-C_0-C_6alkyl, C_0-C_6alkyl-Q-C_6-C_{12}aryl and -Q-C_1-C_6alky;

Q is absent or is selected from the group

-O-, -S(O)$_s$-, -SO$_2$-N(R^n)-, -N(R^n)-SO$_2$-, -N(R^n)-C(=O)-, -C(=O)-N(R^n)-, -N(R^n)-C(=O)-O-, -O-C(=O)-N(R^n)-, -N(R^n)-C(=O)-N(R^n)-, -C(=O)-, -N(R^n)-, -C(=O)-O-, -O-C(=O)-, -het-, -PO(OR^c)O- and -P(O)O-, where s is 0-2; het is a mono- or bicyclic 5, 6, 7, 9 or 10 member heterocyclic ring, each ring containing 1-4 heteroatoms selected from N, O and S, where the heterocyclic ring may be saturated, partially saturated, or aromatic and any N or S being optionally oxidized, the heterocyclic ring being substituted with 0-3 hydroxy, halo(F, Cl, Br, I), CF_3, C_1-C_6alkyl, C_1-C_6alkoxy, nitro and amino;

R^c is selected from hydrogen and substituted or unsubstituted

C_1-C_{10}alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_3-C_{11}cycloalkyl, C_3-C_{10}cycloalkenyl, C_1-C_6alkyl-C_6-C_{12}aryl, C_6-C_{10}aryl-C_1-C_6alkyl, C_1-C_6alkyl-het, het-C_1-C_6alkyl, C_6-C_{12}aryl and het, where the substituents are 1-3 hydroxy. halo(F, Cl, Br, I), CF_3, C_1-C_6alkyl, C_1-C_6alkoxy, nitro and amino;

R^m is selected from

S-C_1-C_6alkyl, C(=O)-C_1-C_6alkyl, C(=O)-$NR^nR^{n'}$, C_1-C_6alkyl, halo(F, Cl, Br, I)-C_1-C_6alkyl, benzyl and phenyl;

R^n is selected from the group

R^c, NH-C(=O)-O-R^c, NH-C(=O)-R^c, NH-C(=O)-NHR^c, NH-SO$_2$-R^s, NH-SO$_2$-NH-C(=O)-R^c, NH-C(=O)-NH-SO$_2$-R^s, C(=O)-O-R^c, C(=O)-R^c, C(=O)-NHR^c, C(=O)-NH-C(=O)-O-R^c, C(=O)-NH-C(=O)-R^c, C(=O)-NH-SO$_2$-R^s, C(=O)-NH-SO$_2$-NHR^s, SO$_2$-R^s, SO$_2$-O-R^s, SO$_2$-N(R^c)$_2$, SO$_2$-NH-C(=O)-O-R^c, SO$_2$-NH-C(=O)-O-R^c and SO$_2$-NH-C(=O)-R^c;

$R^{n'}$ is selected from hydrogen, hydroxy and substituted or unsubstituted

C_1-C_{11}alkyl, C_1-C_{11}alkoxy, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_3-C_{11}cycloalkyl, C_3-C_{10}cycloalkenyl, C_1-C_6alkyl-C_6-C_{12}aryl, C_6-C_{10}aryl-C_1-C_6alkyl, C_6-C_{10}aryl-C_0-C_6alkyloxy, C_1-C_6alkyl-het, het-C_1-C_6alkyl, C_6-C_{12}aryl, het, C_1-C_6alkylcarbonyl, C_1-C_8alkoxycarbonyl, C_3-C_8cycloalkylcarbonyl, C_3-C_8cycloalkoxycarbonyl, C_6-

C_{11}aryloxycarbonyl, C_7-C_{11}arylalkoxycarbonyl, heteroarylalkoxycarbonyl, heteroarylalkylcarbonyl, heteroarylcarbonyl, heteroarylalkylsulfonyl, heteroarylsulfonyl, C_1-C_6alkylsulfonyl and C_6-C_{10}arylsulfonyl, where any alkyl, alkenyl or alkynyl may optionally be substituted with 1-3 groups selected from OH, halo(F, Cl, Br, I), nitro, amino and aminocarbonyl and the substituents on any aryl, heteroaryl or het are 1-2 hydroxy, halo(F, Cl, Br, I), CF_3, C_1-C_6alkyl, C_1-C_6alkoxy, nitro and amino;

R^n and $R^{n'}$ taken together with the common nitrogen to which they are attached may from an optionally substituted heterocycle selected from morpholinyl, piperazinyl, thiamorpholinyl, pyrrolidinyl, imidazolidinyl,indolinyl, isoindolinyl, 1,2,3,4-tetrahydro-quinolinyl, 1,2,3,4-tetrahydro-isoquinolinyl, thiazolidinyl and azabicyclononyl, where the substituents are 1-3 hydroxy, halo(F, Cl, Br, I), CF_3, C_1-C_6alkyl, C_1-C_6alkoxy, nitro and amino;

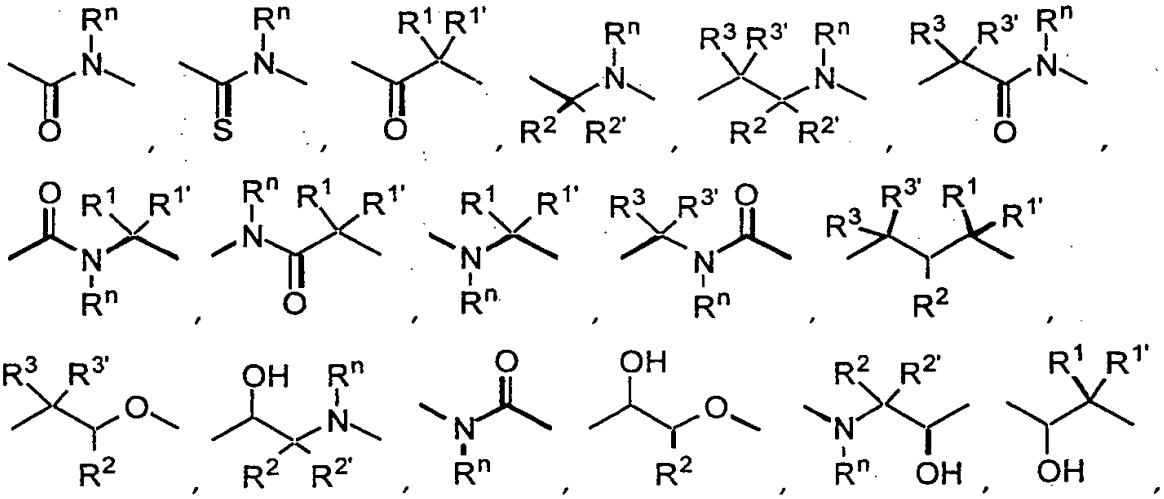
R^s is a substituted or unsubstituted group selected from

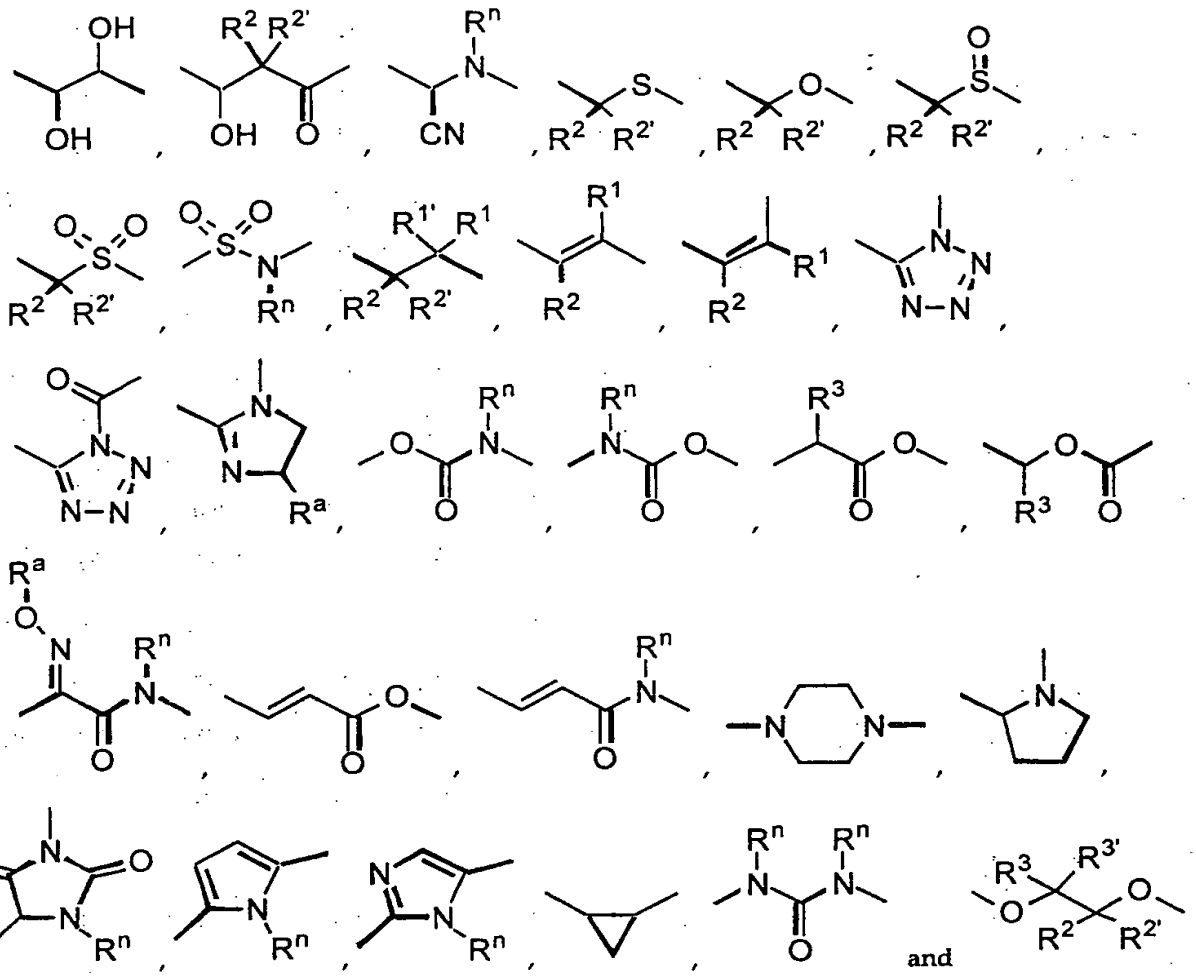
C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, C_3-C_8cycloalkyl, C_3-C_6cycloalkenyl, C_0-C_6alkyl-phenyl, phenyl-C_0-C_6alkyl, C_0-C_6alkyl-het and het-C_0-C_6alkyl, where the substituents are 1-3 hydroxy, halo(F, Cl, Br, I), CF_3, C_1-C_6alkyl, C_1-C_6alkoxy, nitro and amino;

L is selected from the group

$-(CR^6R^{6'})_o$-Ai-$(CR^8R^{8'})_p$-, $-(CR^6R^{6'})_o$-het-$(CR^8R^{8'})_p$-, $-(CR^6{=}CR^7)_q$-Ai-$(CR^8R^{8'})_p$- and $-(CR^6R^{6'})_o$-Ai-$(CR^8{=}CR^9)_r$-,

where Ai is selected from





where o is 0-1, p is 0-1, q is 0-1 and r is 0-1;

R^1, $R^{1'}$, R^2, $R^{2'}$, R^3, $R^{3'}$, R^6, $R^{6'}$, R^7, R^8, $R^{8'}$ and R^9 each are independently selected from R^a, R^c and U-W;

U is an optionally substituted bivalent radical selected from the group

C_1-C_6alkyl-, C_0-C_6alkyl-Q-, C_2-C_6alkenyl-Q-, and C_2-C_6alkynyl-Q-, where the substituents on any alkyl, alkenyl or alkynyl are 1-3 R^a;

W is selected from the group

hydrogen, OH, O-C_1-C_6alkyl, SH, SR^m, $NR^nR^{n'}$, NH-C(=O)-O-R^c, NH-C(=O)-$NR^nR^{n'}$, NH-C(=O)-R^c, NH-SO_2-R^s, NH-SO_2-$NR^nR^{n'}$, NH-SO_2-NH-C(=O)-R^c, NH-C(=O)-NH-SO_2-R^s, C(=O)-NH-C(=O)-O-R^c, C(=O)-NH-C(=O)-R^c, C(=O)-NH-C(=O)-$NR^nR^{n'}$, C(=O)-NH-SO_2-R^s, C(=O)-NH-SO_2-$NR^nR^{n'}$, C(=S)-$NR^nR^{n'}$, SO_2-R^s, SO_2-O-R^s, SO_2-$NR^nR^{n'}$, SO_2-NH-C(=O)-O-R^c, SO_2-NH-C(=O)-$NR^nR^{n'}$, SO_2-NH-C(=O)-R^c, O-C(=O)-$NR^nR^{n'}$, O-C(=O)-

R^C, O-C(=O)-NH-C(=O)-R^C, O-C(=O)-NH-SO_2-R^S and O-SO_2-R^S;

G is hydrogen;

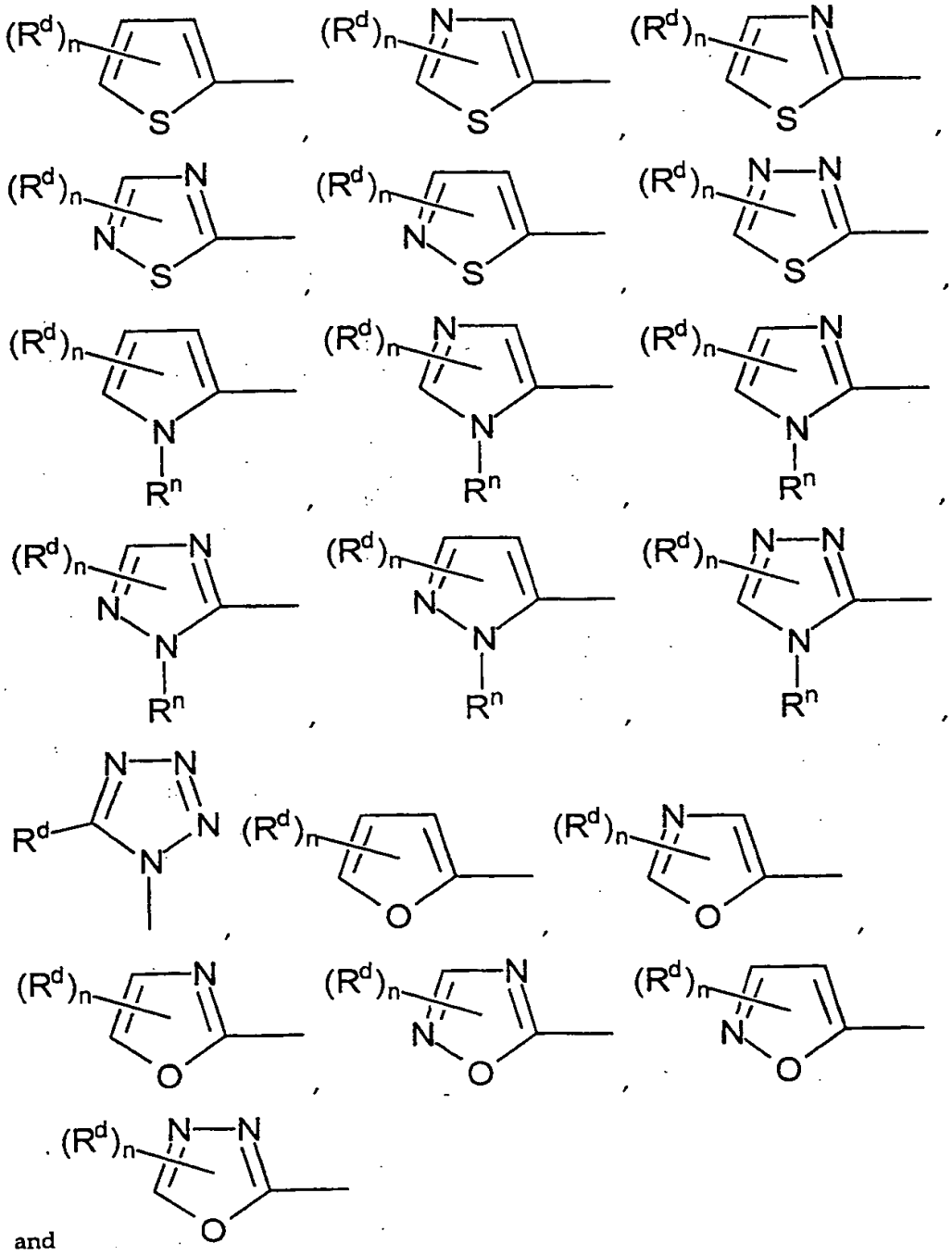
T is U-W;

R is C(=O)-OH and

pharmaceutically acceptable salts thereof.

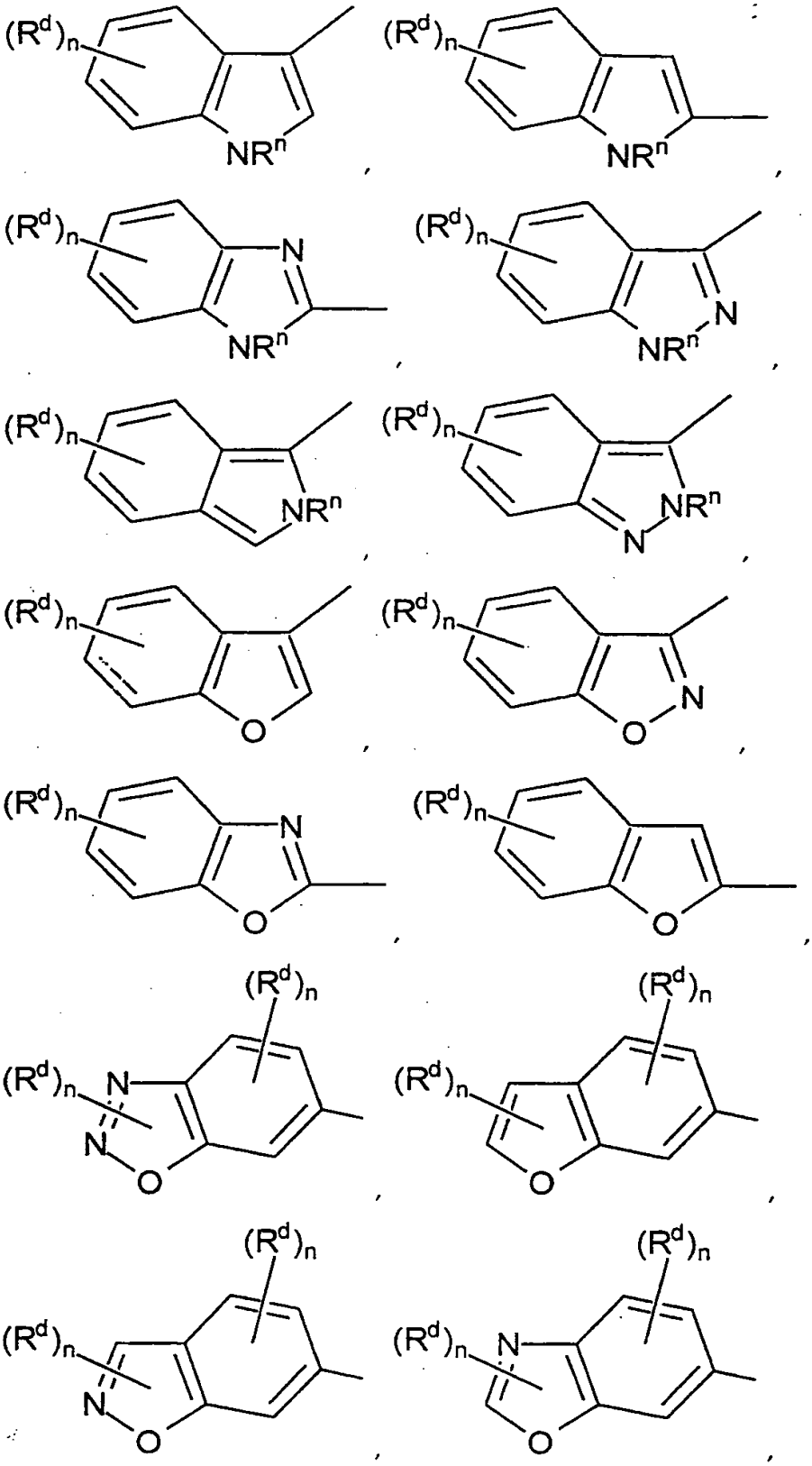
3) The method of Claim 2 wherein D is selected from

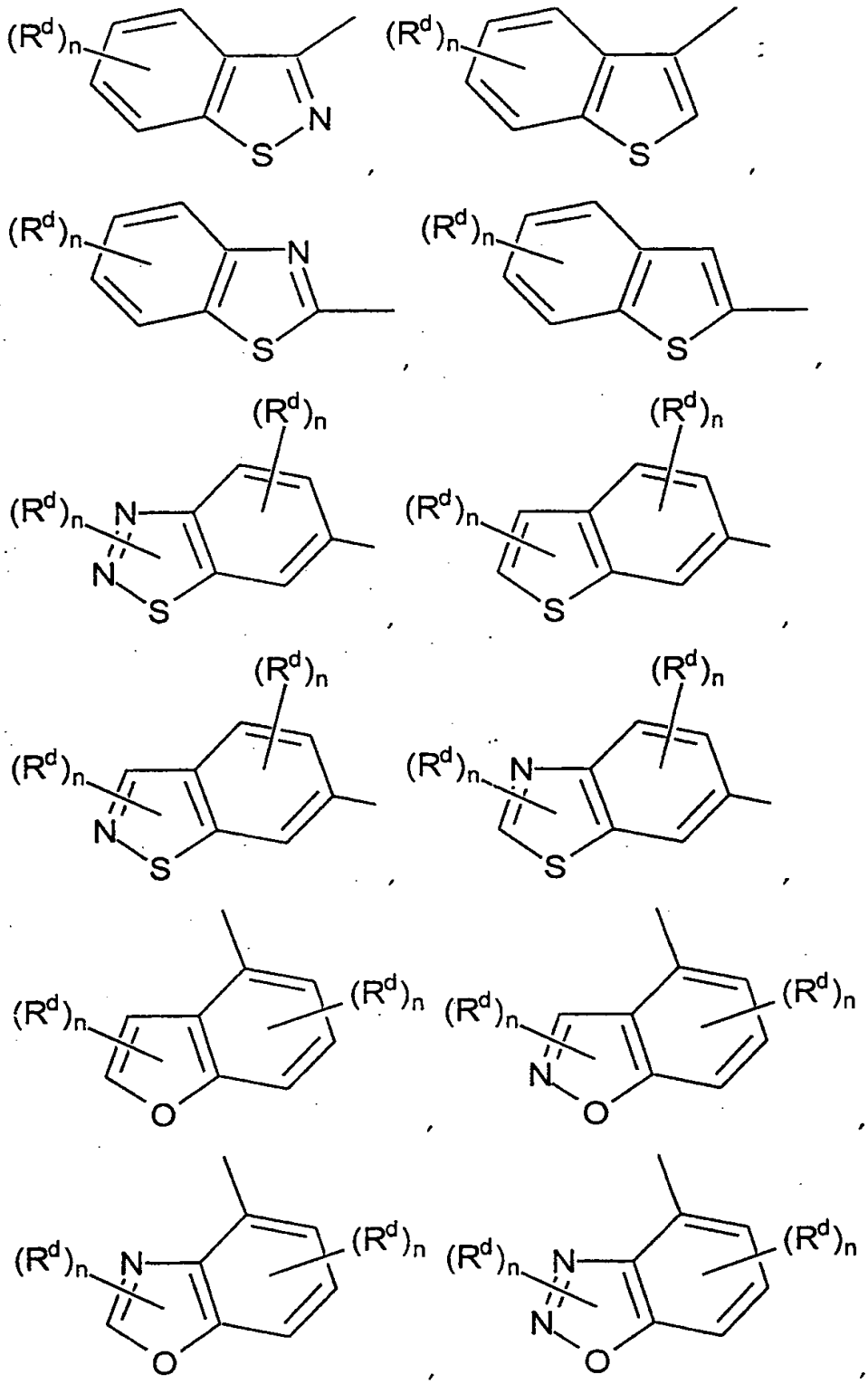
1) a 5-member aromatic heterocycle selected from the group

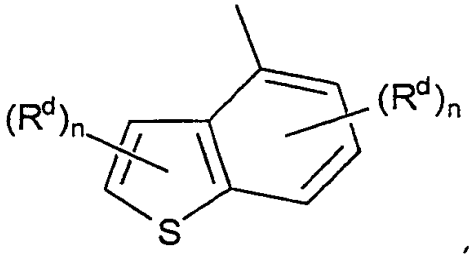
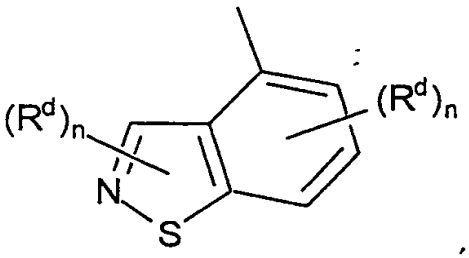
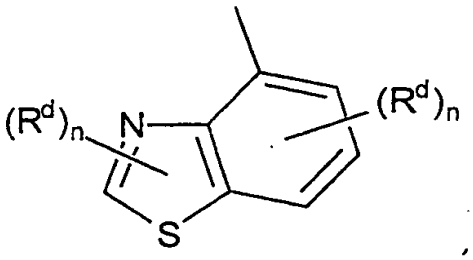
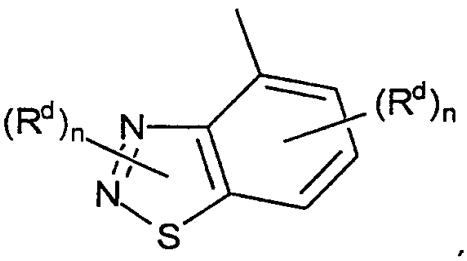


and

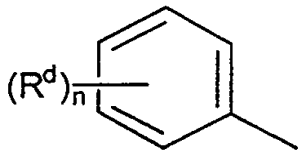
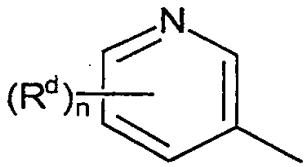
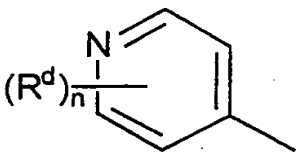
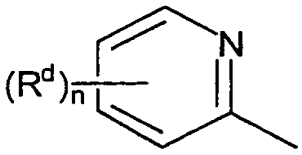
2) a 9-member aromatic heterobicycle selected from the group





3) a 6-member aromatic hetero- or homocycle selected from the group

and ;

L is a bivalent linking group selected from the group

-C_3-C_5-alkyl-,

-C_3-C_5-alkenyl-,

-$CH_2C(=O)NH$-,

-CH_2NH-$C(=O)$-,

-O-CH_2-$C(=O)$-,

-CH_2-CH_2-$C(=O)$-,

-CH=CH-$C(=O)NH$-CH_2-,

-CH=CH-$C(=O)NH$-CH-(CH_3)-,

-CH(OH)-CH_2-O-,

-CH(OH)-CH_2-CH_2-,

-CH_2-CH_2-CH(OH)-,

- $O\text{-}CH_2\text{-}CH(OH)$-,

- $O\text{-}CH_2\text{-}CH(OH)\text{-}CH_2$-,

- $O\text{-}CH_2\text{-}CH_2\text{-}CH(OH)$-,

$-O\text{-}CH_2\text{-}CH_2\text{-}O$-,

$-CH_2\text{-}CH_2\text{-}CH_2\text{-}O$-,

$-CH_2\text{-}CH(OH)\text{-}CH_2\text{-}O$-,

$-CH_2\text{-}CH_2\text{-}O$-,

$-CH\text{-}(CH_3)\text{-}NH\text{-}C(=O)$-,

$-CH_2\text{-}NH\text{-}SO_2$-,

$-NH\text{-}SO_2\text{-}CH_2$-,

$-CH_2\text{-}SO_2NH$-,

$-SO_2NH\text{-}CH_2$-,

$-C(=O)\text{-}NH\text{-}C(=O)$-,

$-NH\text{-}C(=O)\text{-}NH$-,

$-NH\text{-}C(=O)\text{-}NH\text{-}CH_2$-,

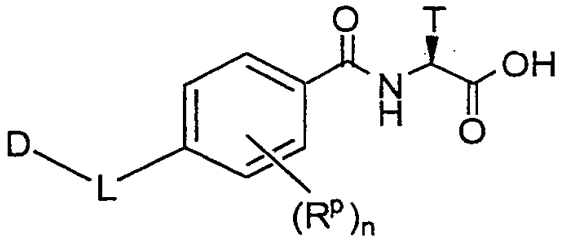
$-CH_2\text{-}NH\text{-}C(=O)\text{-}NH$-,

$-C(=O)\text{-}NH\text{-}CH_2\text{-}C(=O)\text{-}NH$ -,

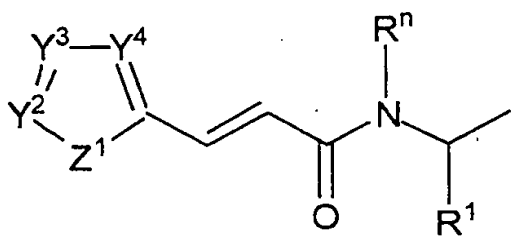
$-NH\text{-}C(=O)\text{-}O$- and

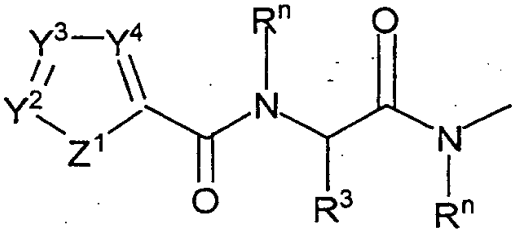
$-O\text{-}C(=O)\text{-}NH$-, and pharmaceutically acceptable salts thereof.

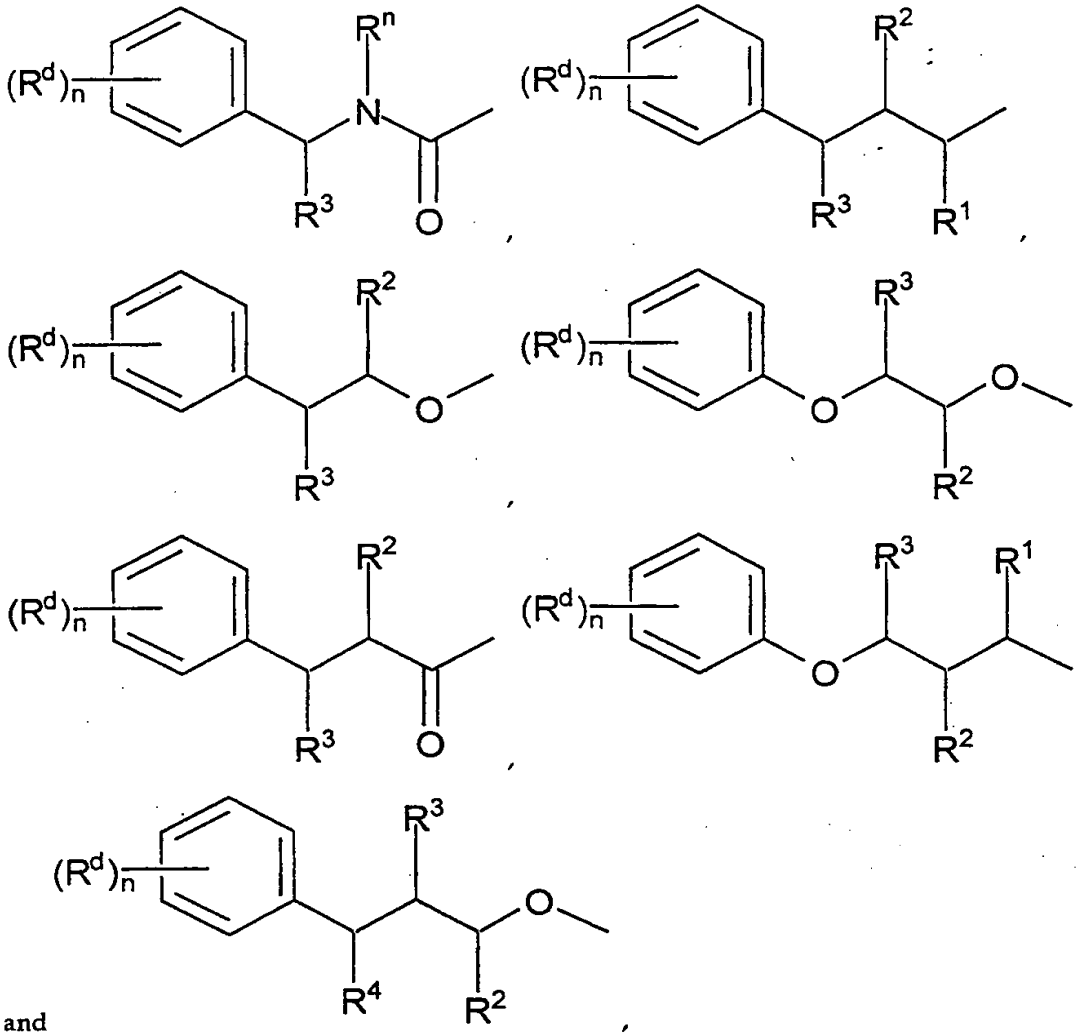
4) The method of Claim 3 wherein the compound is represented by



where D-L- is selected from







and

where

Y^2, Y^3 and Y^4 are selected from the group CH, CR^d and N;

Z^1 is selected from the group O, S, NH and NR^n;

n is 0-3;

R^1, R^2 and R^3 each are independently selected from R^a, R^c and U-W;

U is an optionally substituted bivalent radical selected from the group

C_1-C_6alkyl-, C_0-C_6alkyl-Q-, C_2-C_6alkenyl-Q-, and C_2-C_6alkynyl-Q-, where the substituits on any alkyl, alkenyl or alkynyl are 1-3 R^a;

Q is absent or is selected from the group

-O-, -$S(O)_s$-, -SO_2-$N(R^n)$-, -$N(R^n)$-, -$N(R^n)$-C(=O)-, -$N(R^n)$-C(=O)-$N(R^n)$-, -$N(R^n)$-C(=O)-O-, -O-C(=O)-$N(R^n)$-, -$N(R^n)$-SO_2-, -C(=O)-, -C(=O)-O-, -het-, -C(=O)-$N(R^n)$-, -$PO(OR^c)$O- and -

P(O)O-, where s is 0-2; het is a mono- or bicyclic 5, 6, 7, 9 or 10 member heterocyclic ring, each ring containing 1-4 heteroatoms selected from N, O and S, where the heterocyclic ring may be saturated, partially saturated, or aromatic and any N or S being optionally oxidized, the heterocyclic ring being substituted with 0-3 hydroxy, halo(F, Cl, Br, I), CF_3, C_1-C_6alkyl, C_1-C_6alkoxy, nitro and amino;

W is selected from the group

hydrogen, OH, O-C_1-C_6alkyl, SH, SR^m, $NR^nR^{n'}$, NH-C(=O)-O-R^c, NH-C(=O)-$NR^nR^{n'}$, NH-C(=O)-R^c, NH-SO_2-R^s, NH-SO_2-$NR^nR^{n'}$, NH-SO_2-NH-C(=O)-R^c, NH-C(=O)-NH-SO_2-R^s, C(=O)-NH-C(=O)-O-R^c, C(=O)-NH-C(=O)-R^c, C(=O)-NH-C(=O)-$NR^nR^{n'}$, C(=O)-NH-SO_2-R^s, C(=O)-NH-SO_2-$NR^nR^{n'}$, C(=S)-$NR^nR^{n'}$, SO_2-R^s, SO_2-O-R^s, SO_2-$NR^nR^{n'}$, SO_2-NH-C(=O)-O-R^c, SO_2-NH-C(=O)-$NR^nR^{n'}$, SO_2-NH-C(=O)-R^c, O-C(=O)-$NR^nR^{n'}$, O-C(=O)-R^c, O-C(=O)-NH-C(=O)-R^c, O-C(=O)-NH-SO_2-R^s and O-SO_2-R^s; R^a is $R^{a'}$ or $R^{a''}$ substituted with 1-3 $R^{a'}$; where

$R^{a'}$ is selected from the group

hydrogen, halo(F. Cl, Br, I), cyano, carboxy, carboxy-C_1-C_{11}alkyl, amino, amino-C_1-C_8alkyl, aminocarbonyl, carboxamido, carbamoyl, carbamoyloxy, formyl, formyloxy, azido, nitro, imidazoyl, ureido, thioureido, thiocyanato, hydroxy, C_1-C_6alkoxy, mercapto, sulfonamido, het, phenoxy, phenyl, benzamido, tosyl, morpholino, morpholinyl, piperazinyl, piperidinyl, pyrrolinyl. imidazolyl and indolyl;

$R^{a''}$ is selected from the group

C_0-C_{10}alkyl-Q-C_0-C_6alkyl, C_0-C_{10}alkenyl-Q-C_0-C_6alkyl, C_0-C_{10}alkynyl-Q-C_0-C_6alkyl, C_3-C_{11}cycloalkyl-Q-C_0-C_6alkyl, C_3-C_{10}cycloalkenyl-Q-C_0-C_6alkyl, C_1-C_6alkyl-C_6-C_{12}aryl-Q-C_0-C_6alkyl, C_6-C_{10}aryl-C_1-C_6alkyl-Q-C_0-C_6alkyl, C_0-C_6alkyl-het-Q-C_0-C_6alkyl, C_0-C_6alkyl-Q-het-C_0-C_6alkyl, het-C_0-C_6alkyl-Q-C_0-C_6alkyl, C_0-C_6alkyl-Q-C_6-C_{12}aryl and -Q-C_1-C_6alky;

R^c is selected from hydrogen and substituted or unsubstituted

C_1-C_{10}alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_3-C_{11}cycloalkyl, C_3-C_{10}cycloalkenyl, C_1-C_6alkyl-C_6-C_{12}aryl, C_6-C_{10}aryl-C_1-C_6alkyl, C_1-C_6alkyl-het, het-C_1-C_6alkyl, C_6-C_{12}aryl

and het, where the substituits are 1-3 hydroxy, halo(F, Cl, Br, I), CF_3, C_1-C_6alkyl, C_1-C_6alkoxy, nitro and amino;

R^d is selected from the group

OH, OCF_3, OR^c, SR^m, halo(F, Cl. Br, I), CN, NO_2, CF_3, C_0-C_6alkyl-$NR^nR^{n'}$, C_0-C_6alkyl-C(=O)-$NR^nR^{n'}$, C_0-C_6alkyl-C(=O)-R^a, C_1-C_8alkyl, C_1-C_8alkoxy, C_2-C_8alkenyl, C_2-C_8alkynyl, C_3-C_6cycloalkyl, C_3-C_6cycloalkenyl, C_1-C_6alkyl-phenyl, phenyl-C_1-C_6alkyl, C_1-C_6alkyloxycarbonyl, phenyl-C_0-C_6alkyloxy, C_1-C_6alkyl-het, het-C_1-C_6alkyl, SO_2-het, -O-C_6-C_{12}aryl, -SO_2-C_6-C_{12}aryl, -SO_2-C_1-C_6alkyl and het, where any alkyl, alkenyl or alkynyl may optionally be substituted with 1-3 groups selected from OH, halo(F, Cl, Br, I), nitro, amino and aminocarbonyl and the substituents on any aryl or het are 1-2 hydroxy, halo(F, Cl, Br, I), CF_3, C_1-C_6alkyl, C_1-C_6alkoxy, nitro and amino;

R^m is selected from

S-C_1-C_6alkyl, C(=O)-C_1-C_6alkyl, C(=O)-$NR^nR^{n'}$, C_1-C_6alkyl, halo(F, Cl, Br, I)-C_1-C_6alkyl, benzyl and phenyl;

R^n is selected from the group

R^c, NH-C(=O)-O-R^c, NH-C(=O)-R^c, NH-C(=O)-NHR^c, NH-SO_2-R^s, NH-SO_2-NH-C(=O)-R^c, NH-C(=O)-NH-SO_2-R^s, C(=O)-O-R^c, C(=O)-R^c, C(=O)-NHR^c, C(=O)-NH-C(=O)-O-R^c, C(=O)-NH-C(=O)-R^c, C(=O)-NH-SO_2-R^s, C(=O)-NH-SO_2-NHR^s, SO_2-R^s, SO_2-O-R^s, SO_2-$N(R^c)_2$, SO_2-NH-C(=O)-O-R^c, SO_2-NH-C(=O)-O-R^c and SO_2-NH-C(=O)-R^c;

$R^{n'}$ is selected from hydrogen, hydroxy and substituted or unsubstituted

C_1-C_{11}alkyl, C_1-C_{11}alkoxy, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_3-C_{11}cycloalkyl, C_3-C_{10}cycloalkenyl, C_1-C_6alkyl-C_6-C_{12}aryl, C_6-C_{10}aryl-C_1-C_6alkyl, C_6-C_{10}aryl-C_0-C_6alkyloxy, C_1-C_6alkyl-het, het-C_1-C_6alkyl, C_6-C_{12}aryl, het, C_1-C_6alkylcarbonyl, C_1-C_8alkoxycarbonyl, C_3-C_8cycloalkylcarbonyl, C_3-C_8cycloalkoxycarbonyl, C_6-C_{11}aryloxycarbonyl, C_7-C_{11}arylalkoxycarbonyl, heteroarylalkoxycarbonyl, heteroarylalkylcarbonyl, heteroarylcarbonyl, heteroarylalkylsulfonyl, heteroarylsulfonyl, C_1-C_6alkylsulfonyl and C_6-C_{10}arylsulfonyl, where any alkyl, alkenyl or alkynyl may

optionally be substituted with 1-3 groups selected from OH, halo(F, Cl, Br, I), nitro, amino and aminocarbonyl and the substituents on any aryl, heteroaryl or het are 1-2 hydroxy, halo(F, Cl, Br, I), CF_3, C_1-C_6alkyl, C_1-C_6alkoxy, nitro and amino;

R^n and $R^{n'}$ taken together with the common nitrogen to which they are attached may from an optionally substituted heterocycle selected from morpholinyl, piperazinyl, thiamorpholinyl, pyrrolidinyl, imidazolidinyl,indolinyl, isoindolinyl, 1,2,3,4-tetrahydro-quinolinyl, 1,2,3,4-tetrahydro-isoquinolinyl, thiazolidinyl and azabicyclononyl, where the substituits are 1-3 hydroxy, halo(F, Cl, Br, I), CF_3, C_1-C_6alkyl, C_1-C_6alkoxy, nitro and amino;

R^s is a substituted or unsubstituted group selected from C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, C_3-C_8cycloalkyl, C_3-C_6cycloalkenyl, C_0-C_6alkyl-phenyl, phenyl-C_0-C_6alkyl, C_0-C_6alkyl-het and het-C_0-C_6alkyl, where the substituits are 1-3 hydroxy, halo(F, Cl, Br, I), CF_3, C_1-C_6alkyl, C_1-C_6alkoxy, nitro and amino;

T is U-W; and

pharmaceutically acceptable salts thereof.

5) The method of Claim 4 wherein

Y^2, Y^3 and Y^4 are selected from CH and CR^d;

Z^1 is selected from NR^n, O and S;

n is 0-3;

R^1, R^2 and R^3 each are independently R^a;

R^a is $R^{a'}$ or $R^{a''}$ substituted with 1-3 $R^{a'}$; where

$R^{a'}$ is selected from the group hydrogen, halo(F. Cl, Br, I), cyano, carboxy, carboxy, amino, amino, aminocarbonyl, carboxamido, carbamoyl, carbamoyloxy, formyl, formyloxy, azido, nitro, imidazoyl, ureido, thioureido, thiocyanato, hydroxy, C_1-C_6alkoxy, mercapto, sulfonamido, phenoxy, phenyl, benzamido, morpholino, morpholinyl, piperazinyl, piperidinyl, pyrrolinyl. imidazolyl and indolyl;

$R^{a''}$ is hydrogen or a substituted or unsubstituted group selected from C_0-C_{10}alkyl-het, C_1-C_{10}alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_3-C_{11}cycloalkyl, C_3-C_{10}cycloalkenyl-C_0-C_6alkyl, C_1-C_6alkyl-C_6-C_{12}aryl and C_6-C_{10}aryl-C_1-C_6alkyl, where the substituits are 1-3 hydroxy, halo(F, Cl, Br, I), CF_3, C_1-C_6alkyl, C_1-C_6alkoxy, nitro and

amino;

R^d is selected from the group

OH, OCF_3, $OR^{a''}$, SR^m, halo(F, Cl. Br, I), CN, NO_2, CF_3, C_0-C_6alkyl-C(=O)-R^a, C_1-C_8alkyl, C_1-C_8alkoxy, C_2-C_8alkenyl, C_2-C_8alkynyl, C_3-C_6cycloalkyl, phenyl-C_1-C_6alkyl, C_1-C_6alkyloxycarbonyl, -O-C_6-C_{12}aryl and -SO_2-C_6-C_{12}aryl, where any alkyl, alkenyl or alkynyl may optionally be substituted with 1-3 groups selected from OH, halo(F, Cl, Br, I), nitro, amino and aminocarbonyl and the substituents on any aryl or het are 1-2 hydroxy, halo(F, Cl, Br, I), CF_3, C_1-C_6alkyl, C_1-C_6alkoxy, nitro and amino;

R^m is selected from

S-C_1-C_6alkyl, C(=O)-C_1-C_6alkyl, C(=O)-NH_2, C_1-C_6alkyl, halo(F, Cl, Br, I)-C_1-C_6alkyl, benzyl and phenyl;

R^n is selected from the group

$R^{a''}$, NH-C(=O)-O-$R^{a''}$, NH-C(=O)-$R^{a''}$, NH-C(=O)-$NHR^{a''}$, NH-SO_2-R^s, NH-SO_2-NH-C(=O)-$R^{a''}$, NH-C(=O)-NH-SO_2-R^s, C(=O)-O-$R^{a''}$, C(=O)$R^{a''}$, C(=O)-$NHR^{a''}$, C(=O)-NH-C(=O)-O-$R^{a''}$, C(=O)-NH-C(=O)-$R^{a''}$, C(=O)-NH-SO_2-R^s, C(=O)-NH-SO_2-NHR^s, SO_2-R^s, SO_2-O-R^s, SO_2-$N(R)_2$, SO_2-NH-C(=O)-O-$R^{a''}$, SO_2-NH-C(=O)-O-$R^{a''}$ and SO_2-NH-C(=O)-$R^{a''}$;

$R^{n'}$ is selected from hydrogen, hydroxy and substituted or unsubstituted

C_1-C_{11}alkyl, C_1-C_{11}alkoxy, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_3-C_{11}cycloalkyl, C_3-C_{10}cycloalkenyl, C_1-C_6alkyl-C_6-C_{12}aryl, C_6-C_{10}aryl-C_1-C_6alkyl, C_6-C_{10}aryl-C_0-C_6alkyloxy, C_1-C_6alkyl-het, het-C_1-C_6alkyl, C_6-C_{12}aryl, het, C_1-C_6alkylcarbonyl, C_1-C_8alkoxycarbonyl, C_3-C_8cycloalkylcarbonyl, C_3-C_8cycloalkoxycarbonyl, C_6-C_{11}aryloxycarbonyl, C_7-C_{11}arylalkoxycarbonyl, heteroarylalkoxycarbonyl, heteroarylalkylcarbonyl, heteroarylcarbonyl, heteroarylalkylsulfonyl, heteroarylsulfonyl, C_1-C_6alkylsulfonyl and C_6-C_{10}arylsulfonyl, where any alkyl, alkenyl or alkynyl may optionally be substituted with 1-3 groups selected from OH, halo(F, Cl, Br, I), nitro, amino and aminocarbonyl and the substituents on any aryl, heteroaryl or het are 1-2 hydroxy, halo(F, Cl, Br, I), CF_3, C_1-C_6alkyl, C_1-C_6alkoxy, nitro and amino;

R^n and $R^{n'}$ taken together with the common nitrogen to which they are attached may from an optionally substituted heterocycle selected from morpholinyl, piperazinyl, thiamorpholinyl, pyrrolidinyl, imidazolidinyl,indolinyl, isoindolinyl, 1,2,3,4-tetrahydro-quinolinyl, 1,2,3,4-tetrahydro-isoquinolinyl, thiazolidinyl and azabicyclononyl, where the substituits are 1-3 hydroxy, halo(F, Cl, Br, I), CF_3, C_1-C_6alkyl, C_1-C_6alkoxy, nitro and amino;

R^s is a substituted or unsubstituted group selected from C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, C_3-C_8cycloalkyl, C_3-C_6cycloalkenyl, C_0-C_6alkyl-phenyl, phenyl-C_0-C_6alkyl, C_0-C_6alkyl-het and het-C_0-C_6alkyl, where the substituits are 1-3 hydroxy, halo(F, Cl, Br, I), CF_3, C_1-C_6alkyl, C_1-C_6alkoxy, nitro and amino; T is U-W, where

U is an optionally substituted bivalent radical selected from the group C_1-C_6alkyl-Q-, C_2-C_6alkenyl-Q-, and C_2-C_6alkynyl-Q-, where the substituits on any alkyl, alkenyl or alkynyl are 1-3 R^a;

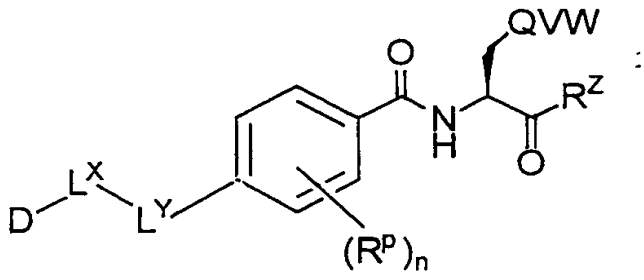
Q is absent or is selected from the group

$-SO_2-N(R^n)-$, $-N(R^n)-$, $-N(R^n)-C(=O)-$, $-N(R^n)-C(=O)-O-$, $-N(R^n)-SO_2-$, $-C(=O)-N(R^n)-$ $C(=O)-O-$, $-C(=O)-O-$, $-C(=O)-$ and $-C(=O)-N(R^n)-$;

W is selected from the group

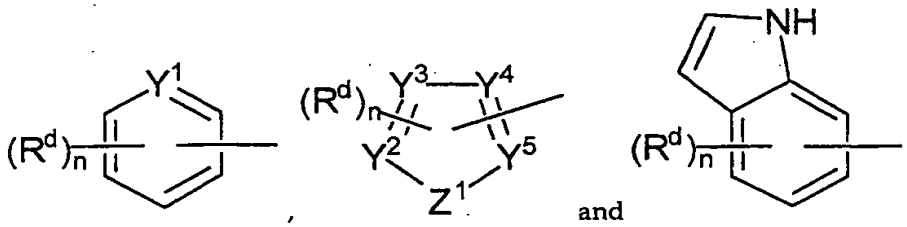
hydrogen, OH, O-C_1-C_6alkyl, SH, SR^m, $NR^nR^{n'}$, $NH-C(=O)-O-R^{a''}$, $NH-C(=O)-NR^nR^{n'}$, $NH-C(=O)-R^{a''}$, $NH-SO_2-R^s$, $NH-SO_2-NR^nR^{n'}$, $NH-SO_2-NH-C(=O)-R^{a''}$, $NH-C(=O)-NH-SO_2-R^s$, $C(=O)-NH-C(=O)-O-R^{a''}$, $C(=O)-NH-C(=O)-R^{a''}$, $C(=O)-NH-C(=O)-NR^nR^{n'}$, $C(=O)-NH-SO_2-R^s$, $C(=O)-NH-SO_2-NR^nR^{n'}$, $C(=S)-NR^nR^{n'}$, SO_2-R^s, SO_2-O-R^s, $SO_2-NR^nR^{n'}$, $SO_2-NH-C(=O)-O-R^{a''}$, $SO_2-NH-C(=O)-NR^nR^{n'}$, $SO_2-NH-C(=O)-R^{a''}$, $O-C(=O)-NR^nR^{n'}$, $O-C(=O)-R^{a''}$, $O-C(=O)-NH-C(=O)-R^{a''}$, $O-C(=O)-NH-SO_2-R^s$ and $O-SO_2-R^s$; and pharmaceutically acceptable salts thereof.

6) A method of treating mammal having an immune disorder mediated through the CD11/CD18 family of adhesion receptors comprising the step of administering a pharmacologically effective amount of a compound represented by the formula:



where

D is selected from the group



and

where

Y^1 is selected from the group NR^n, CH and CR^d;

Y^2, Y^3, Y^4 and Y^5 are selected from the group CH and CR^d;

Z^1 is selected from the group NR^n, O and S;

n is 0-3;

L^X is selected from the group substituted or unsubstituted

C_2-C_5alkylene,

C_3-C_6cycloalkylene,

C_0-C_3alkylene-NR^n-(C=O)-C_0-C_3alkylene,

C_0-C_3alkylene-(C=O)-NR^n-C_0-C_3alkylene,

C_0-C_3alkylene-O-C_0-C_3alkylene,

C_0-C_3alkylene-NR^n-C_0-C_3alkylene,

C_0-C_3alkylene-(C=O)-C_0-C_3alkylene,

C_0-C_3alkylene-$S(O)_{0-2}$-C_0-C_3alkylene,

C_0-C_3alkylene-NR^n-SO_2-C_0-C_3alkylene,

C_0-C_3alkylene-SO_2-NR^n-C_0-C_3alkylene,

C_0-C_3alkylene-CR^1=CR^2-C_0-C_3alkylene,

C_0-C_3alkylene-C≡C-C_0-C_3alkylene and

C_0-C_3alkylene-het-C_0-C_3alkylene

where the substituents are selected from the group one to three R^1, R^2 and R^3;

L^Y is selected from the group substituted or unsubstituted

C_0-C_2alkylene,

C_0-C_2alkylene-NR^n-(C=O)-C_0-C_2alkylene,

C_0-C_2alkylene-(C=O)-NR^n-C_0-C_2alkylene,

C_0-C_2alkylene-O-C_0-C_2alkylene,

C_0-C_2alkylene-NR^n-C_0-C_2alkylene,

C_0-C_2alkylene-(C=O)-C_0-C_2alkylene,

C_0-C_3alkylene-$S(O)_{0-2}$-C_0-C_3alkylene,

C_0-C_3alkylene-SO_2-NR^n-C_0-C_3alkylene and

C_0-C_2alkylene-aryl-C_0-C_2alkylene

where the substituents are selected from the group one to three R^1, R^2 and R^3;

R^1, R^2 and R^3 are selected from the group

hydrogen,

C_1-C_8alkyl-hydroxy,

halo(F, Cl, Br, I),

halo(F, Cl, Br, I)-C_1-C_8alkyl,

cyano,

isocyanate,

carboxy,

carboxy-C_1-C_6alkyl,

amino,

amino-C_1-C_8alkyl,

amino-di(C_1-C_8alkyl),

aminocarbonyl,

carboxamido,

carbamoyl,

carbamoyloxy,
formyl,
formyloxy,
nitro,
imidazoyl,
ureido,
thioureido,
thiocyanato,
hydroxy,
C_1-C_6alkoxy,
mercapto,
sulfonamido,
phenoxy,
phenyl, and
benzamido;

R^a is selected from the group
hydrogen,
halo(F. Cl, Br, I),
cyano,
isocyanate,
carboxy,
carboxy-C_1-C_6alkyl,
amino,
amino-C_1-C_8alkyl,
aminocarbonyl,
carboxamido,
carbamoyl,
carbamoyloxy,
formyl,
formyloxy,
azido,
nitro,
imidazoyl,
ureido,
thioureido,
thiocyanato,

hydroxy,
C_1-C_6alkoxy,
mercapto,
sulfonamido,
C_1-C_6alkylsulfonyl,
het,
phenoxy,
phenyl,
benzamido,
tosyl,
morpholino,
morpholinyl,
piperazinyl,
piperidinyl,
pyrrolinyl.
imidazolyl and
indolyl;

R^c is selected from hydrogen and substituted or unsubstituted
C_1-C_{10}alkyl,
C_2-C_{10}alkenyl,
C_2-C_{10}alkynyl,
C_3-C_{11}cycloalkyl,
C_3-C_{10}cycloalkenyl,
C_1-C_6alkyl-C_6-C_{12}aryl,
C_6-C_{10}aryl-C_1-C_6alkyl,
C_1-C_6alkyl-het,
het-C_1-C_6alkyl,
C_6-C_{12}aryl,
C_1-C_{10}alkyl-O-,
C_2-C_{10}alkenyl-O-,
C_2-C_{10}alkynyl-O-,
C_3-C_{11}cycloalkyl-O-,

C_3-C_{10}cycloalkenyl-O-,

C_1-C_6alkyl-C_6-C_{12}aryl-O-,

C_6-C_{10}aryl-C_1-C_6alkyl-O-,

C_1-C_6alkyl-het-O-,

het-C_0-C_6alkyl-O-,

C_6-C_{12}aryl-O-

C_1-C_{10}alkyl-NR^n-,

C_2-C_{10}alkenyl-NR^n-,

C_2-C_{10}alkynyl-NR^n-,

C_3-C_{11}cycloalkyl-NR^n-,

C_3-C_{10}cycloalkenyl-NR^n-,

C_1-C_6alkyl-C_6-C_{12}aryl-NR^n-,

C_6-C_{10}aryl-C_1-C_6alkyl-NR^n-,

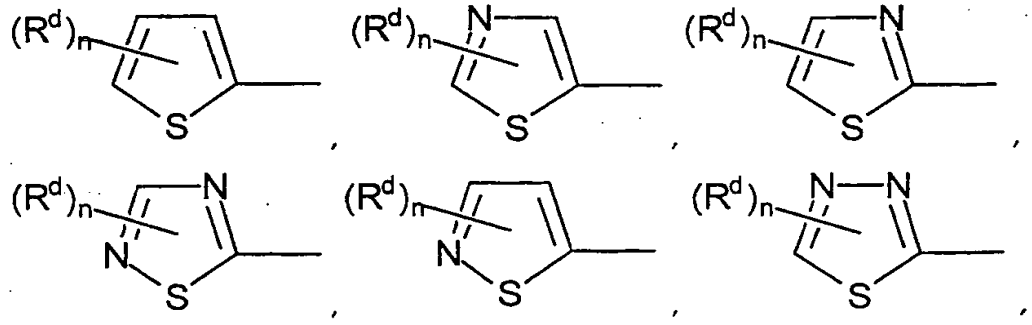
C_1-C_6alkyl-het-NR^n-,

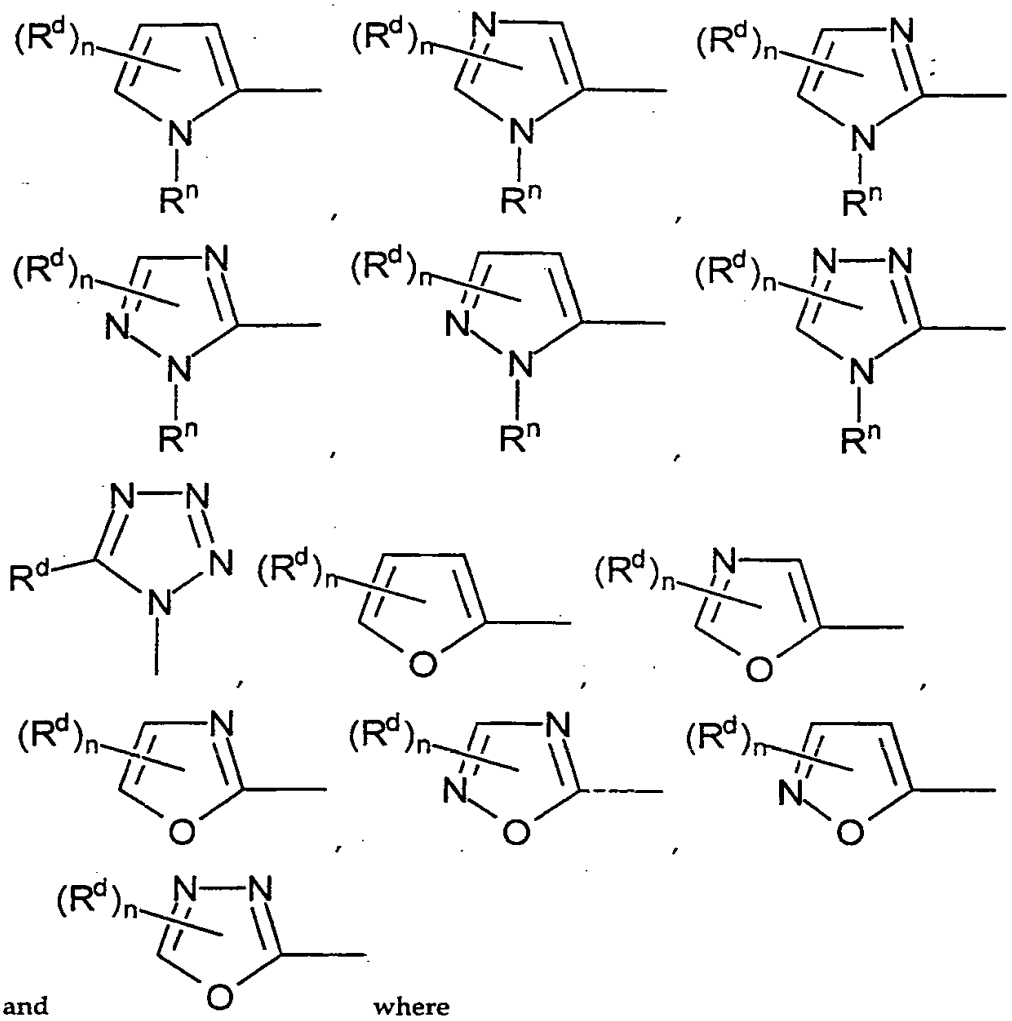
het-C_0-C_6alkyl-NR^n-,

C_6-C_{12}aryl-NR^n- and

het, where the substituents on any alkyl, alkenyl or alkynyl are 1-3 R^a and the substituents on any aryl or het are 1-3 R^d;

het is selected from the group





and where

R^p and R^d are independently selected from the group

OH,

CN,

NO_2,

halo(F, Cl. Br, I),

OR^n,

SR^n,

SOR^n,

CF_3,

R^c,

$NR^nR^{n'}$,

$NR^n C(=O)-O-R^{n'}$,

$NR^nC(=O)-R^{n'}$,

C_0-C_6alkyl-SO_2-R^n,

C_0-C_6alkyl-SO_2-$NR^nR^{n'}$,

$C(=O)-R^n$,

$O-C(=O)-R^n$,

$C(=O)-O-R^n$ and

$C(=O)-NR^nR^{n'}$,

R^d is a chemical bond when het is a divalent linking group;

R^n and $R^{n'}$ are independently selected from the group

hydrogen,

hydroxy,

C_1-C_6alkyl,

halo(F, Cl, Br, I)-C_1-C_6alkyl,

C_1-C_6alkyl-het,

het-C_1-C_6alkyl,

C_6-C_{12}aryl, and

het;

R^z is a substituted or unsubstituted group selected from

hydroxy,

C_1-C_{11}alkoxy,

C_3-C_{12}cycloalkoxy,

C_8-C_{12}aralkoxy,

C_8-C_{12}arcycloalkoxy,

C_6-C_{10}aryloxy,

C_3-C_{10}alkylcarbonyloxyalkyloxy,

C_3-C_{10}alkoxycarbonyloxyalkyloxy,

C_3-C_{10}alkoxycarbonylalkyloxy,

C_5-C_{10}cycloalkylcarbonyloxyalkyloxy,

C_5-C_{10}cycloalkoxycarbonyloxyalkyloxy,

C_5-C_{10}cycloalkoxycarbonylalkyloxy,

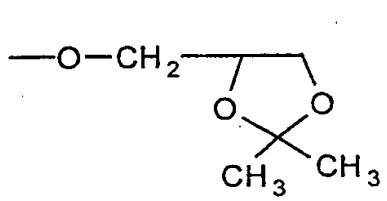
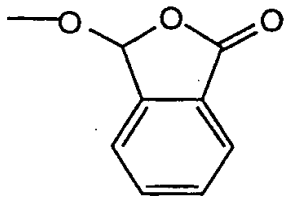
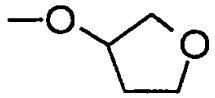
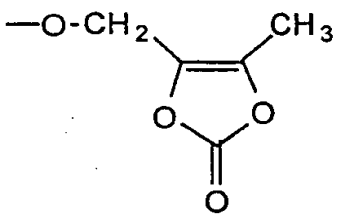
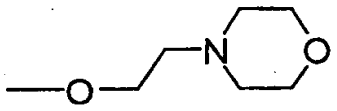
C_8-C_{12}aryloxycarbonylalkyloxy,

C_8-C_{12}aryloxycarbonyloxyalkyloxy,

C_8-C_{12}arylcarbonyloxyalkyloxy,

C_5-C_{10}alkoxyalkylcarbonyloxyalkyloxy,

$(R^n)(R^{n'})N(C_1$-C_{10}alkoxy)-,






and

where the substituents on any alkyl, alkenyl or alkynyl are 1-3 R^a and the substituents on any aryl or het are 1-3 R^d;

Q is absent or is C_0-C_3 alkyl substituted with a group selected from

$-N(R^n)-$,

$-N(R^n)-C(=O)-$,

$-N(R^n)-C(=O)-O-$,

$-N(R^n)-C(=O)-N(R^n)-$,

$-N(R^n)-SO_2-$,

$-C(=O)-$,

$-O-C(=O)-N(R^n)-$,

$-C(=O)-N(R^n)-$,

V is absent or is an optionally substituted bivalent group selected from

C_1-C_{11}alkylene,

C_0-C_3alkylene-O-C_0-C_3alkylene,

C_2-C_6alkenylene,

C_0-C_2alkylene-O-C_2-C_4alkenylene,

C_3-C_8cycloalkylene,

C_6-C_{10}aryl-C_0-C_6alkylene,

C_0-C_6alkyl-C_6-C_{10}arylene and

C_0-C_6alky-het;

where the substituents on any alkyl are 1-3 R^a and the substituents on any aryl or het are 1-3 R^d;

W is a C_0-C_3 -alkyl substituted with a group selected from

R^a,

NH-C(=O)-$NR^nR^{n'}$,

NH-C(=O)-R^c,

C(=O)-R^c,

C(=O)-NH-C(=O)-R^c,

C(=O)-NH-C(=O)-$NR^nR^{n'}$,

C(=O)-NH-SO_2- R^c,

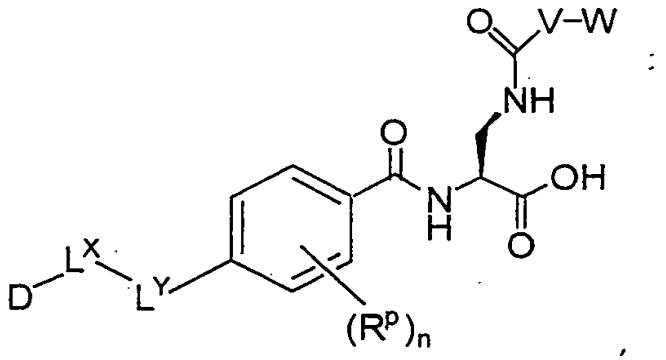
C(=O)-NH-SO_2-$NR^nR^{n'}$,

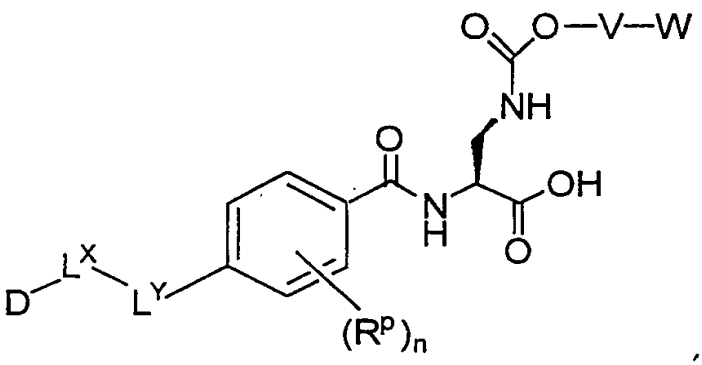
C(=O)$NR^nR^{n'}$,

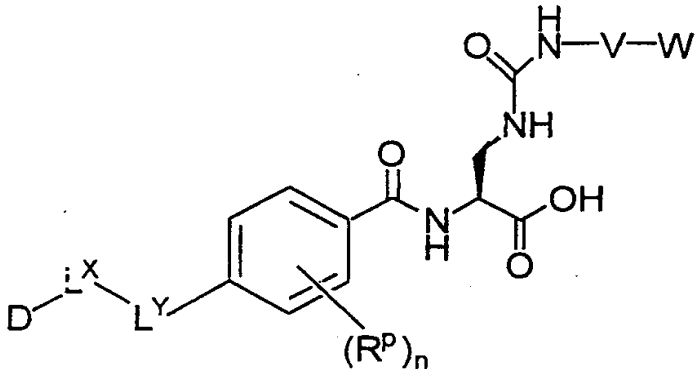
NH-C(=O)-R^c and

R^c and pharmaceutically acceptable salts thereof.

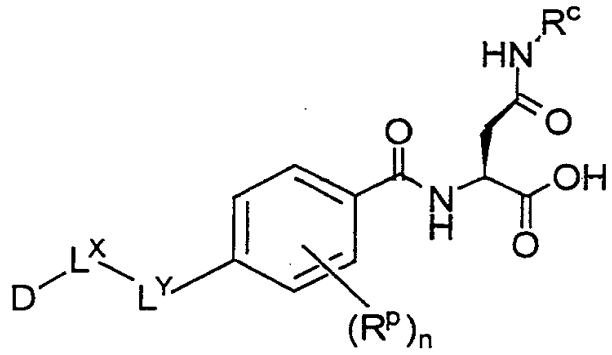
7) The method of Claim 6 wherein the compound selected from the group





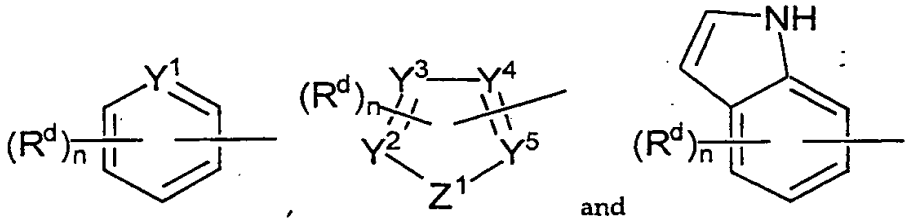


and



where

D is selected from the group



and

where Y^1, Y^2, Y^3, Y^4 and Y^5 are selected from the group CH and CR^d;

Z^1 is selected from the group NR^n, O and S;

n is 0-3;

L^X is selected from the group substituted or unsubstituted

C_2-C_5alkylene,

C_3-C_6cycloalkylene,

C_0-C_3alkylene-NR^n-(C=O)-C_0-C_3alkylene,

C_0-C_3alkylene-(C=O)-NR^n-C_0-C_3alkylene,

C_0-C_3alkylene-O-C_0-C_3alkylene,

C_0-C_3alkylene-NR^n-C_0-C_3alkylene,

C_0-C_3alkylene-(C=O)-C_0-C_3alkylene,

C_0-C_3alkylene-$S(O)_{0-2}$-C_0-C_3alkylene,

C_0-C_3alkylene-NR^n-SO_2-C_0-C_3alkylene,

C_0-C_3alkylene-SO_2-NR^n-C_0-C_3alkylene,

C_0-C_3alkylene-CR^1=CR^2-C_0-C_3alkylene,

C_0-C_3alkylene-C≡C-C_0-C_3alkylene and

C_0-C_3alkylene-het-C_0-C_3alkylene

where the substituits are selected from the group one to three R^1, R^2 and R^3;

L^Y is selected from the group substituted or unsubstituted

C_0-C_2alkylene,

C_0-C_2alkylene-NR^n-(C=O)-C_0-C_2alkylene,

C_0-C_2alkylene-(C=O)-NR^n-C_0-C_2alkylene,

C_0-C_2alkylene-O-C_0-C_2alkylene,

C_0-C_2alkylene-NR^n-C_0-C_2alkylene,

C_0-C_2alkylene-(C=O)-C_0-C_2alkylene,

C_0-C_3alkylene-$S(O)_{0-2}$-C_0-C_3alkylene,

C_0-C_3alkylene-SO_2-NR^n-C_0-C_3alkylene and

C_0-C_2alkylene-aryl-C_0-C_2alkylene

where the substituits are selected from the group one to three R^1, R^2 and R^3;

R^1, R^2 and R^3 are selected from the group

hydrogen,

C_1-C_8alkyl-hydroxy,

halo(F, Cl, Br, I),

halo(F, Cl, Br, I)-C_1-C_8alkyl,

cyano,

isocyanate,

carboxy,

carboxy-C_1-C_{11}alkyl,

amino,

amino-C_1-C_8alkyl,

amino-di(C_1-C_8alkyl),

aminocarbonyl,

carboxamido,

carbamoyl,

carbamoyloxy,

formyl,

formyloxy,

azido,

nitro,

imidazoyl,

ureido,

thioureido,

thiocyanato,

hydroxy,

C_1-C_6alkoxy,

mercapto,

sulfonamido,

phenoxy,

phenyl, and

benzamido;

R^a is selected from the group

hydrogen,

halo(F. Cl, Br, I),

carboxy,

amino,

amino-C_1-C_8alkyl,

aminocarbonyl,

carboxamido,

carbamoyl,

carbamoyloxy,

formyl,

formyloxy,

imidazoyl,

ureido,

hydroxy,

C_1-C_6alkoxy,

sulfonamido,

het,

phenoxy and

phenyl,

R^c is selected from hydrogen and substituted or unsubstituted

C_1-C_{10}alkyl,

C_2-C_{10}alkenyl,

C_2-C_{10}alkynyl,

C_3-C_{11}cycloalkyl,

C_3-C_{10}cycloalkenyl,

C_1-C_6alkyl-C_6-C_{12}aryl,

C_6-C_{10}aryl-C_1-C_6alkyl,

C_1-C_6alkyl-het,

het-C_1-C_6alkyl,

C_6-C_{12}aryl,

C_1-C_{10}alkyl-O-,

C_2-C_{10}alkenyl-O-,

C_2-C_{10}alkynyl-O-,

C_3-C_{11}cycloalkyl-O-,

C_3-C_{10}cycloalkenyl-O-,

C_1-C_6alkyl-C_6-C_{12}aryl-O-,

C_6-C_{10}aryl-C_1-C_6alkyl-O-,

C_1-C_6alkyl-het-O-,

het-C_0-C_6alkyl-O-,

C_6-C_{12}aryl-O-

C_1-C_{10}alkyl-NR^n-,

C_2-C_{10}alkenyl-NR^n-,

C_2-C_{10}alkynyl-NR^n-,

C_3-C_{11}cycloalkyl-NR^n-,

C_3-C_{10}cycloalkenyl-NR^n-,

C_1-C_6alkyl-C_6-C_{12}aryl-NR^n-,

C_6-C_{10}aryl-C_1-C_6alkyl-NR^n-,

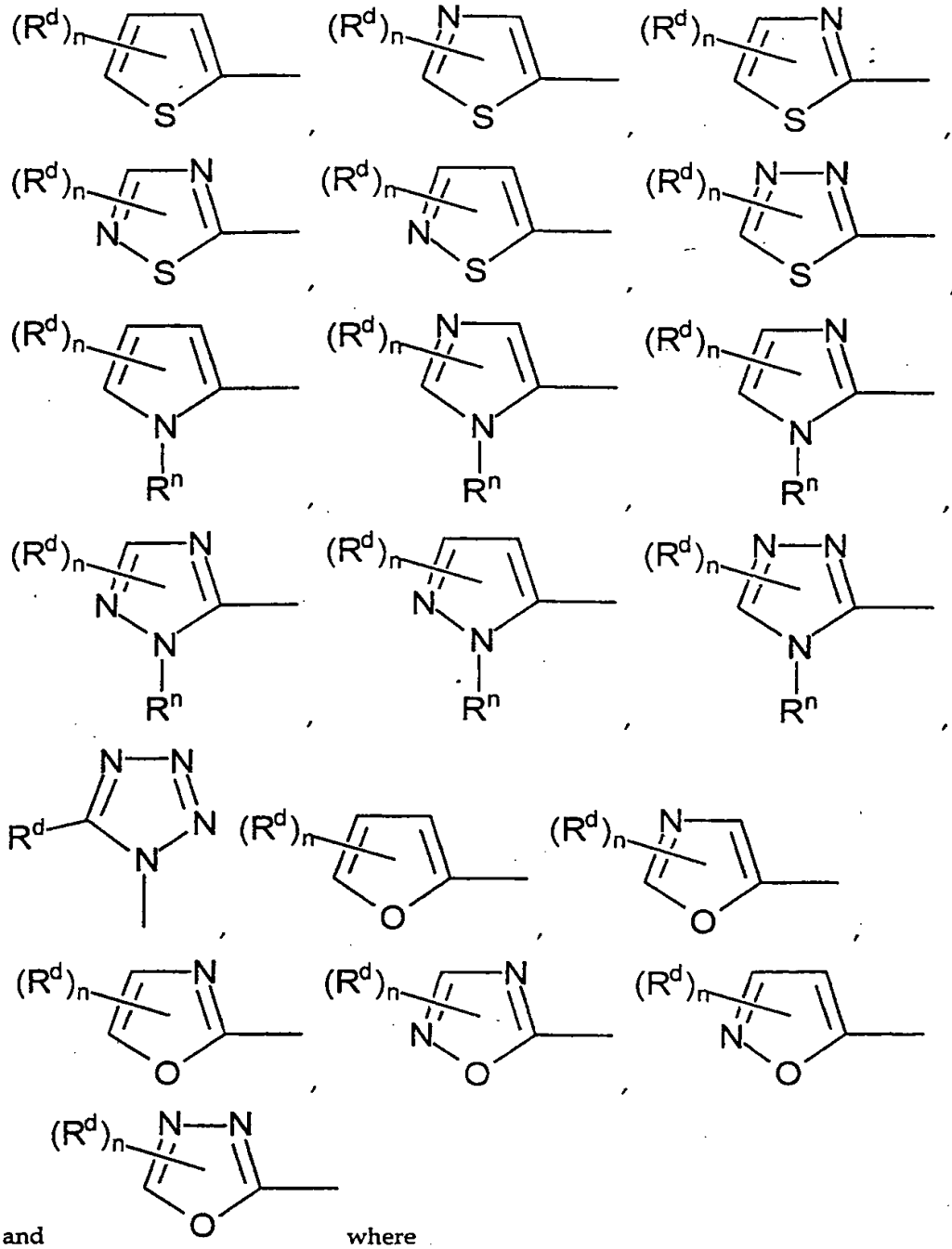
C_1-C_6alkyl-het-NR^n-,

het-C_0-C_6alkyl-NR^n-,

C_6-C_{12}aryl-NR^n- and het, where the substituents on any alkyl, alkenyl or alkynyl are 1-3 R^a

and the substituents on any aryl or het are 1-3 R^d;

het is selected from the group



and where

R^p and R^d are independently selected from the group

OH,

CN,

NO_2,

halo(F, Cl. Br, I),

OR^n,

SR^n,

SOR^n,

CF_3,

R^c,

$NR^nR^{n'}$,

$NR^n C(=O)-O-R^{n'}$,

$NR^n C(=O)-R^{n'}$,

C_0-C_6alkyl-SO_2-R^n,

C_0-C_6alkyl-SO_2-$NR^nR^{n'}$,

$C(=O)-R^n$,

$O-C(=O)-R^n$,

$C(=O)-O-R^n$ and

$C(=O)-NR^nR^{n'}$,

R^d is a chemical bond when het is a divalent linking group;

R^n and $R^{n'}$ are independently selected from the group

hydrogen,

hydroxy,

C_1-C_6alkyl and

halo(F, Cl. Br, I)-C_1-C_6alkyl;

V is absent or is an optionally substituted bivalent group selected from

C_1-C_6alkylene,

C_0-C_3alkylene-O-C_0-C_3alkylene,

C_2-C_6alkenylene,

C_0-C_2alkylene-O-C_2-C_4alkenylene,

C_3-C_8cycloalkylene,

C_0-C_6alkyl-C_6-C_{10}arylene and

C_0-C_6alky-het;

where the substituents on any alkyl are 1-3 R^a and the substituents on any aryl or het are 1-3 R^d;

W is selected from the group

hydrogen,

$NH\text{-}C(=O)\text{-}NR^nR^{n'}$,

$NH\text{-}C(=O)\text{-}R^c$,

$C(=O)\text{-}NH\text{-}C(=O)\text{-}R^c$,

$C(=O)\text{-}NH\text{-}C(=O)\text{-}NR^nR^{n'}$,

$C(=O)\text{-}NH\text{-}SO_2\text{-}R^c$,

$C(=O)\text{-}NH\text{-}SO_2\text{-}NR^nR^{n'}$,

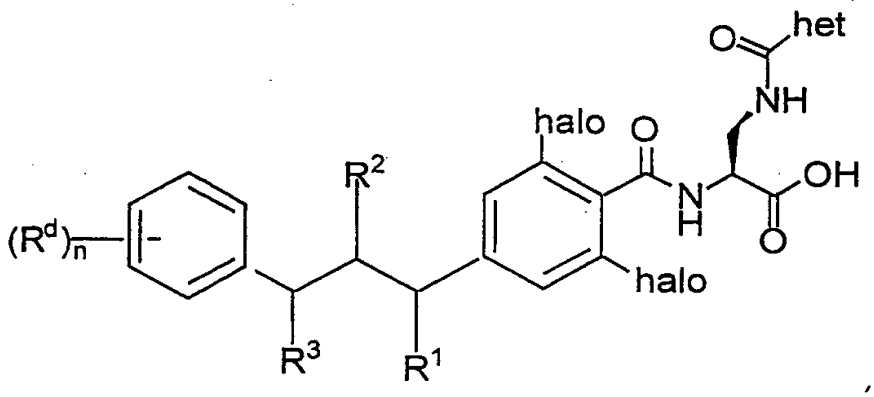
$C(=O)NR^nR^{n'}$,

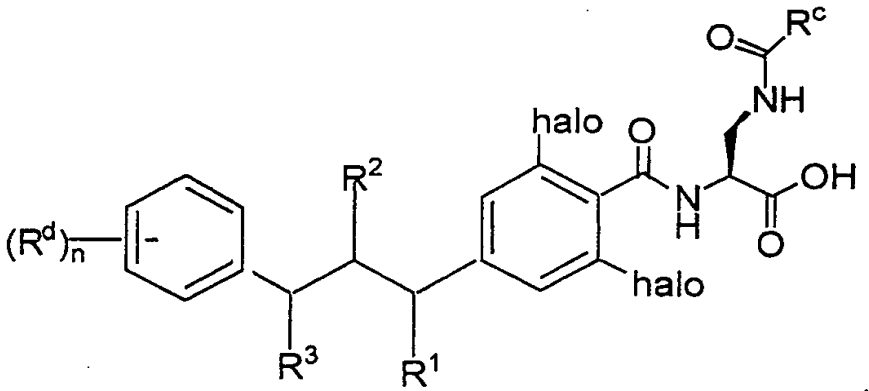
$NH\text{-}C(=O)\text{-}R^c$ and

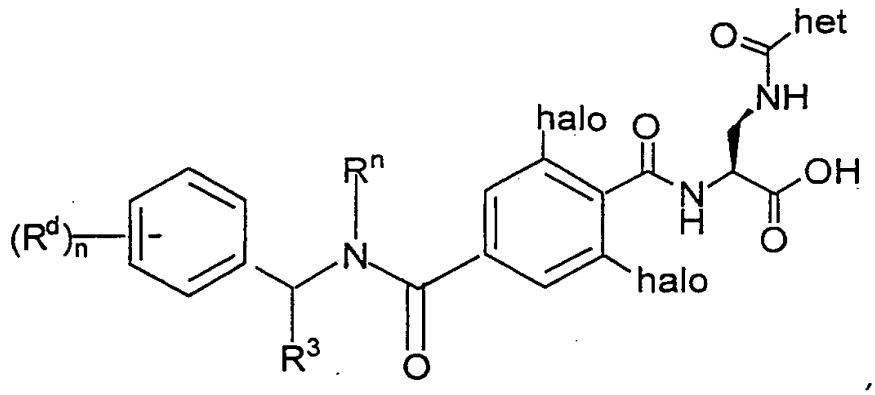
R^d; and

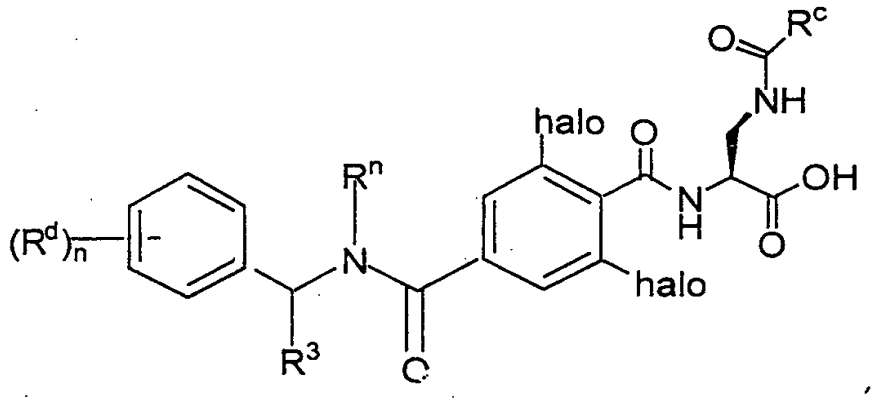
pharmaceutically acceptable salts thereof.

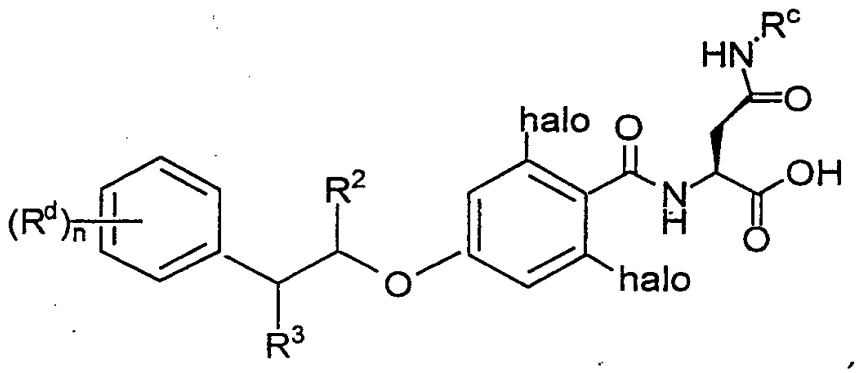
8) The method of Claim 6 wherein the compound is selected from the group

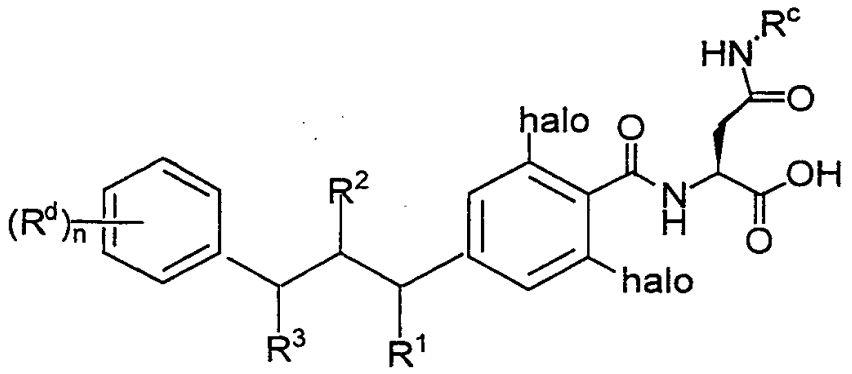


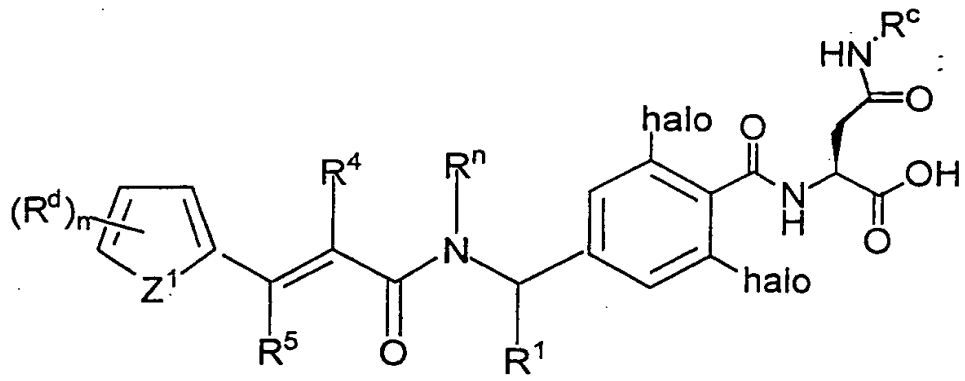


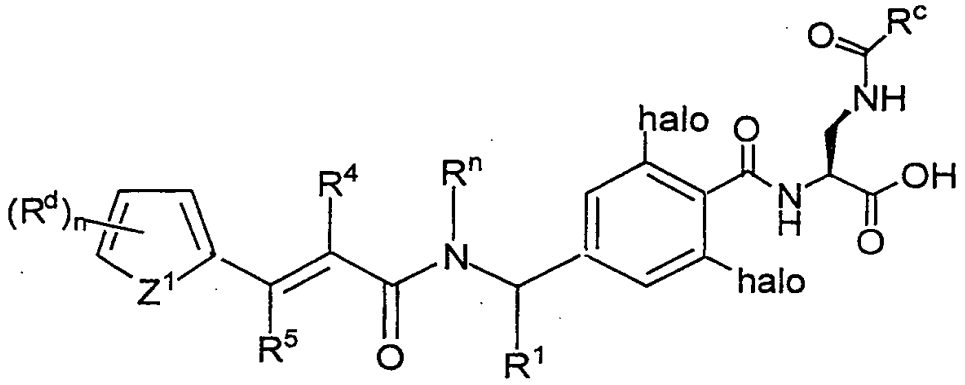




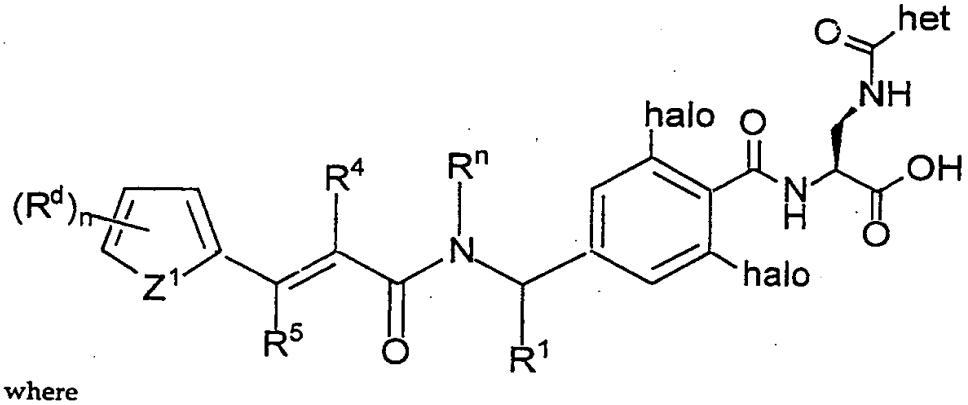








and



where

R^1, R^2, R^3, R^4,and R^5 are selected from the group

hydrogen,

C_1-C_8alkyl,

C_1-C_8alkyl-hydroxy,

halo(F, Cl, Br, I),

halo(F, Cl, Br, I)-C_1-C_8alkyl,

amino,

amino-C_1-C_8alkyl,

aminocarbonyl-C_0-C_6alkyl,

amino-di(C_1-C_8alkyl),

carboxamido,

carbamoyl,

carbamoyloxy,

formyl,

formyloxy,

ureido,

hydroxy,

C_1-C_6alkoxy,

sulfonamido,

phenyl and

phenoxy,

R^a is selected from the group

hydrogen,

halo(F. Cl. Br, I),

cyano,

isocyanate,

carboxy,

amino,

amino-C_1-C_8alkyl,

aminocarbonyl,

carboxamido,

carbamoyl,

carbamoyloxy,

formyl,

formyloxy,

imidazoyl,

ureido,

hydroxy,

C_1-C_6alkoxy,

sulfonamido,

phenoxy and

phenyl,

R^c is selected from hydrogen and substituted or unsubstituted

C_1-C_{10}alkyl,

C_2-C_{10}alkenyl,

C_2-C_{10}alkynyl,

C_3-C_{11}cycloalkyl,

C_3-C_{10}cycloalkenyl,

C_1-C_6alkyl-C_6-C_{12}aryl,

C_6-C_{10}aryl-C_1-C_6alkyl,

C_1-C_6alkyl-het,

het-C_1-C_6alkyl,

C_6-C_{12}aryl,

C_1-C_{10}alkyl-O-,

C_2-C_{10}alkenyl-O-,

C_2-C_{10}alkynyl-O-,

C_3-C_{11}cycloalkyl-O-,

C_3-C_{10}cycloalkenyl-O-,

C_1-C_6alkyl-C_6-C_{12}aryl-O-,

C_6-C_{10}aryl-C_1-C_6alkyl-O-,

C_1-C_6alkyl-het-O-,

het-C_0-C_6alkyl-O-,

C_6-C_{12}aryl-O-

C_1-C_{10}alkyl-NR^n-,

C_2-C_{10}alkenyl-NR^n-,

C_2-C_{10}alkynyl-NR^n-,

C_3-C_{11}cycloalkyl-NR^n-,

C_3-C_{10}cycloalkenyl-NR^n-,

C_1-C_6alkyl-C_6-C_{12}aryl-NR^n-,

C_6-C_{10}aryl-C_1-C_6alkyl-NR^n-,

C_1-C_6alkyl-het-NR^n-,

het-C_0-C_6alkyl-NR^n-,

C_6-C_{12}aryl-NR^n- and

het, where the substituents on any alkyl, alkenyl or alkynyl are 1-3 R^a and the substituents on any aryl or het are 1-3 R^d;

R^d are independently selected from the group

OH,

C_1-C_6alkyl,

halo(F, Cl. Br, I),

NO_2,

cyano,

OR^n,

SR^n,

SOR^n,

CF_3,

R^c,

$NR^nR^{n'}$,

$NR^n C(=O)$-O-$R^{n'}$,

$NR^n C(=O)$-$R^{n'}$,

C_0-C_6alkyl-SO_2-R^n,

C_0-C_6alkyl-SO_2-$NR^nR^{n'}$,

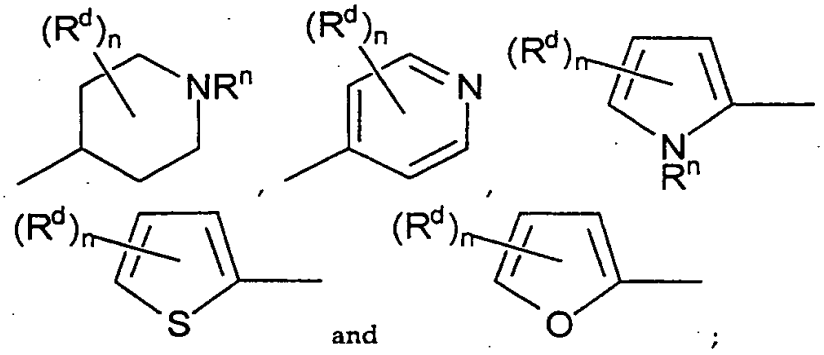
$C(=O)$-R^n,

O-$C(=O)$-R^n,

$C(=O)$-O-R^n and

$C(=O)$-$NR^nR^{n'}$,

het is selected from the group



and ;

R^n and $R^{n'}$ are independently selected from the group

hydrogen,

hydroxyl,

C_1-C_6alkyl and

halo(F, Cl. Br, I)-C_1-C_6alkyl;

halo is selected from the group F and Cl;

Z^1 is selected from the group NR^n, O and S;

n is 0-3; and

pharmaceutically acceptable salts thereof.

9) The method of Claim 6 wherein the adhesion receptor is selected from LFA-1 (CD11a/CD18) and Mac-1 (CD11b/CD18).

10) The method of Claim 9 wherein the adhesion receptor is LFA-1.

11) The method of Claim 6 wherein the immune disorder is selected from the group; rejection of or by a transplanted graft, psoriasis, rheumatoid arthritis. asthma and multiple sclerosis.

12) The method of Claim 6 further comprising administering an effective amount of an immunosuppressive agent to the mammal.

13) The method of Claim 6 further comprising administering an effective amount of a VLA-4 antagonist to the mammal.

14) The method of Claim 10 wherein the disorder is selected from psoriasis and asthma and the therapeutically effective amount of the LFA-1 antagonist is administered orally, topically, transdermally, inter-pulmonary or inter-nasal.

15) The method of Claim 6 wherein the mammal is a human.

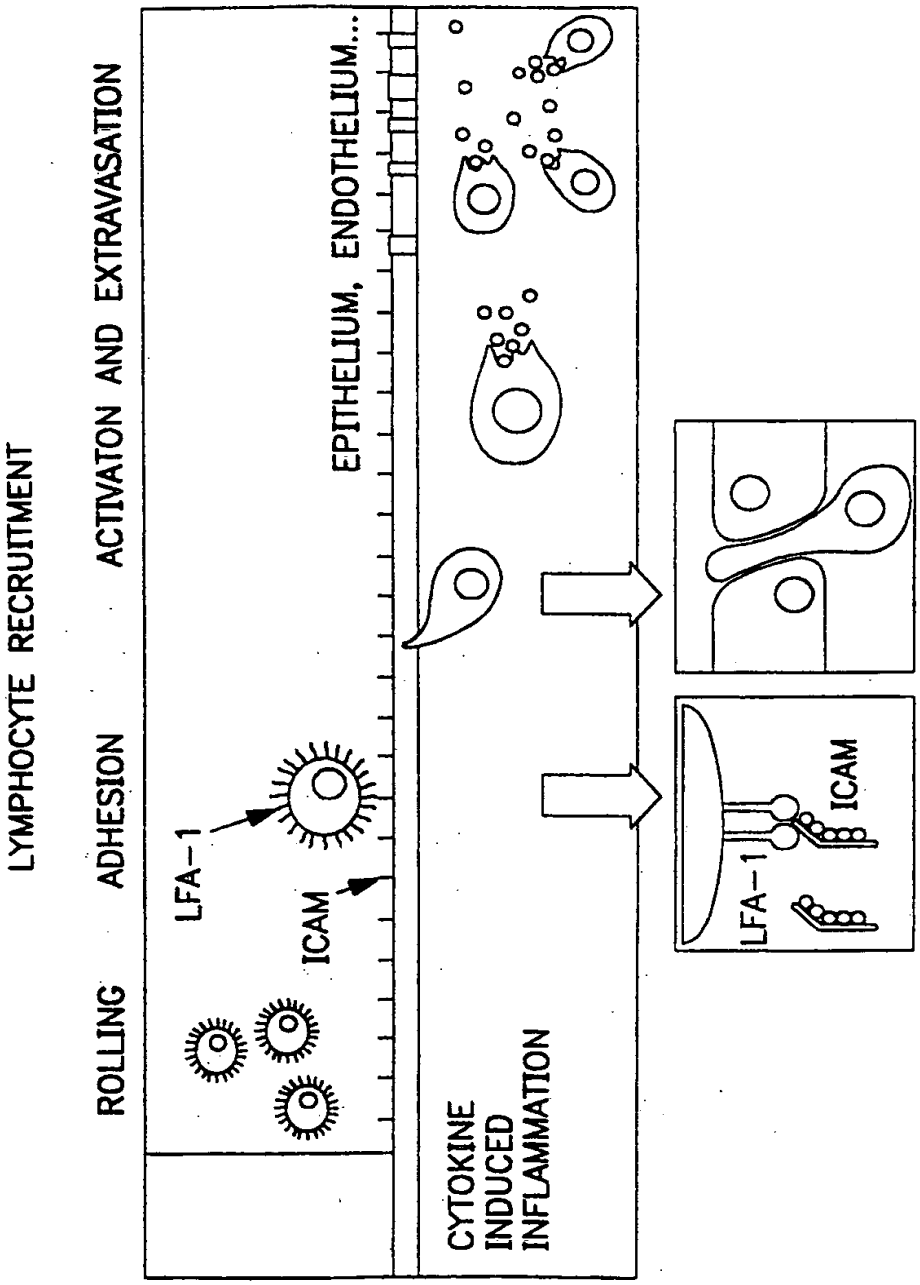

LYMPHOCYTE RECRUITMENT
ROLLING
ADHESION
ACTIVATON AND EXTRAVASATION
LFA-1
ICAM
EPITHELIUM, ENDOTHELIUM...
CYTOKINE INDUCED INFLAMMATION
LFA-1
ICAM

FIG. 1

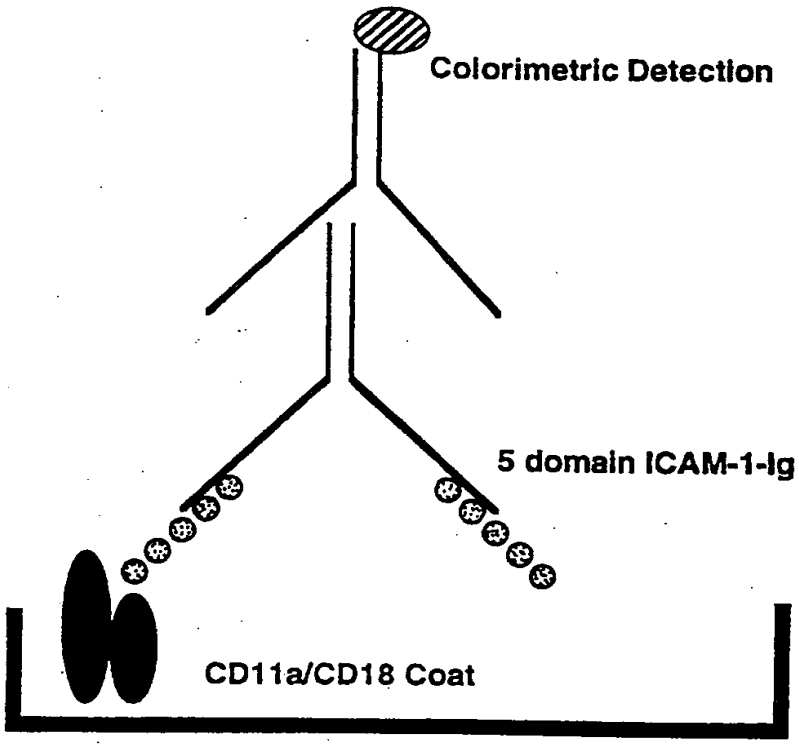

Human ICAM-1:LFA-1 Receptor Binding Assay
Colorimetric Detection
5 domain ICAM-1-Ig
CD11a/CD18 Coat

FIG. 2

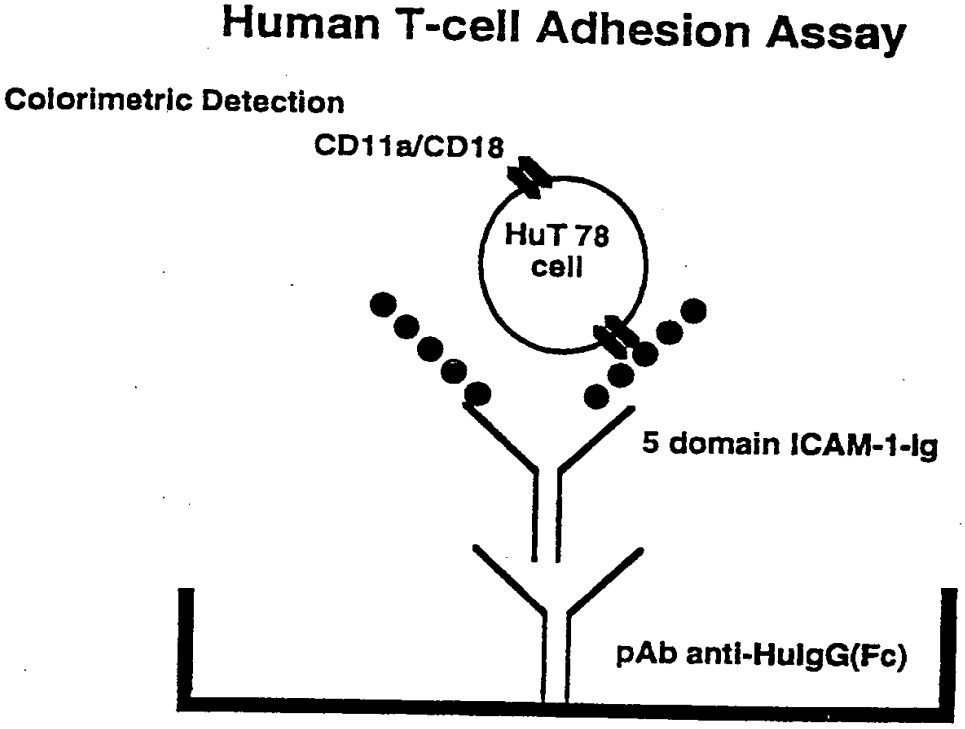

Human T-cell Adhesion Assay
Colorimetric Detection
CD11a/CD18
HuT 78 cell
5 domain ICAM-1-Ig
pAb anti-HuIgG(Fc)

FIG. 3

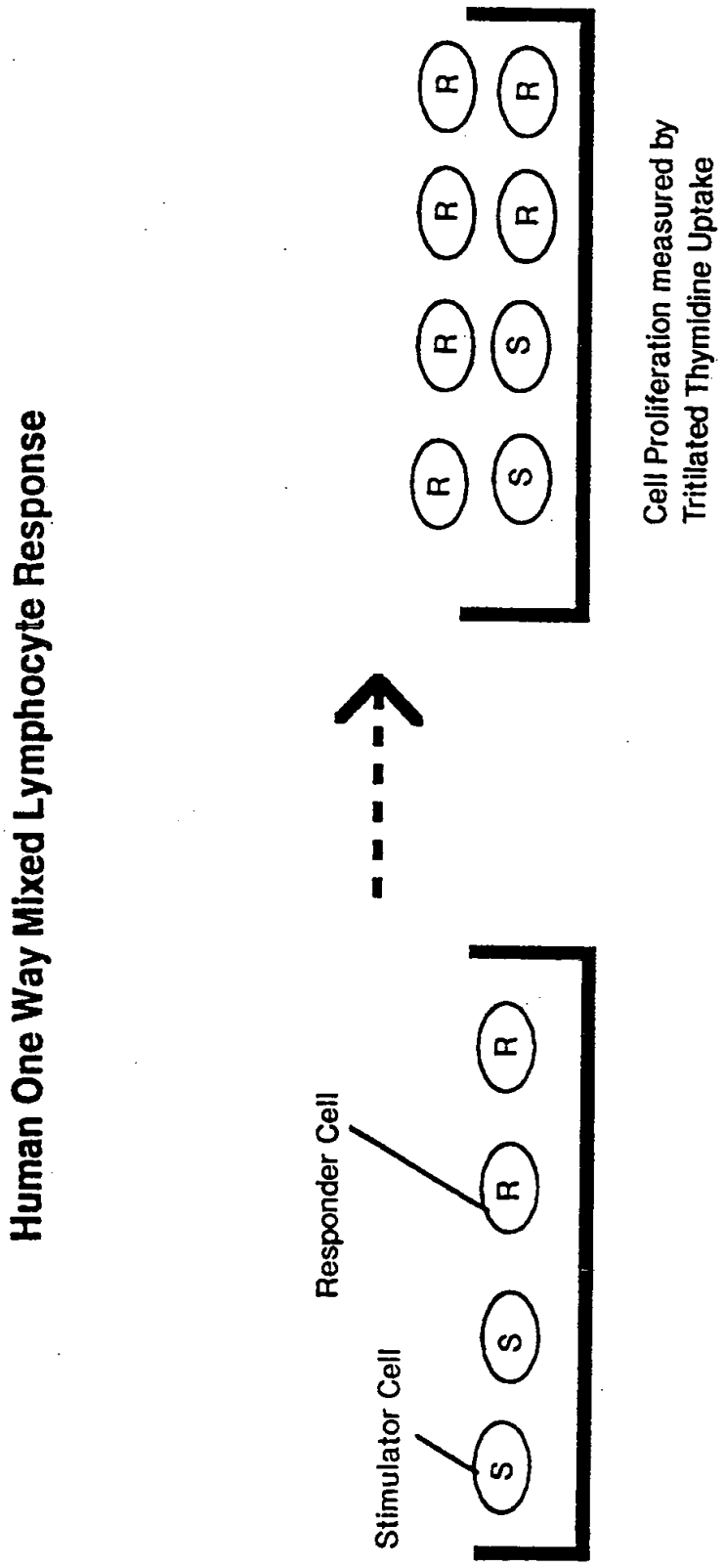

Human One Way Mixed Lymphocyte Response
Responder Cell
Stimulator Cell
S
S
R
R
R
S
R
R
R
S
R
R
Cell Proliferation measured by
Tritilated Thymidine Uptake

FIG. 4

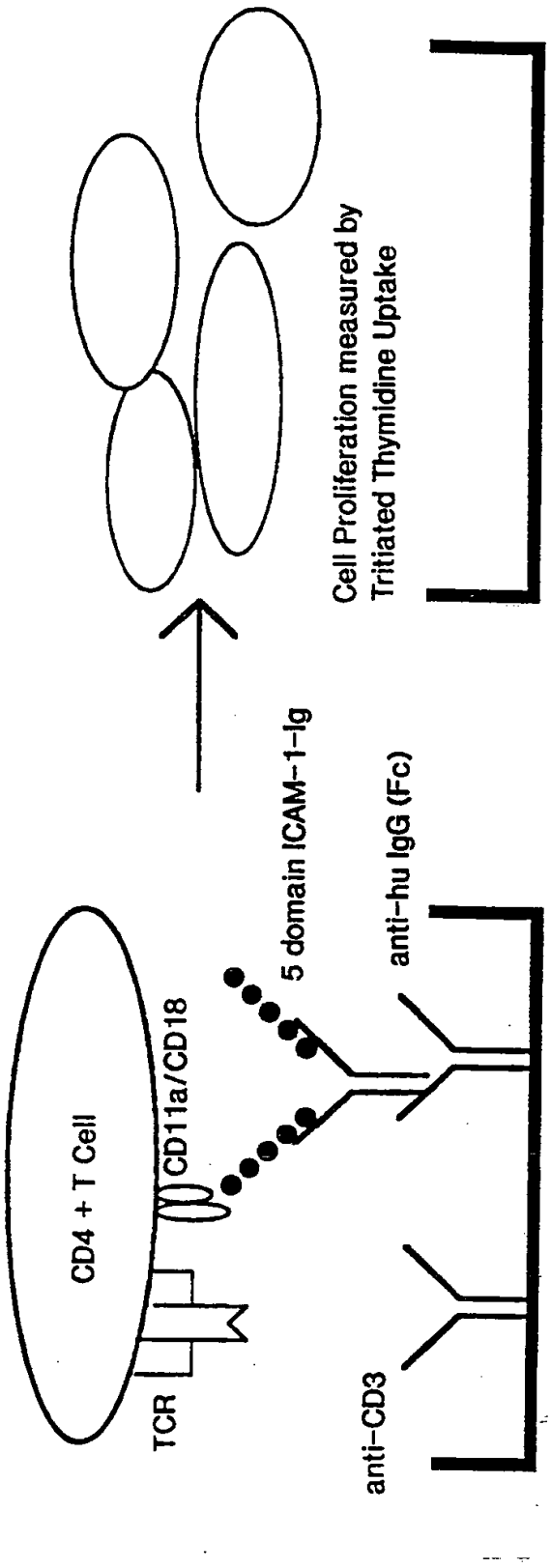

CD4 + T Cell
CD11a/CD18
5 domain ICAM-1-Ig
anti-hu IgG (Fc)
TCR
anti-CD3
Cell Proliferation measured by
Tritiated Thymidine Uptake
Coat anti-Fc 2 ug/ml & anti-CD3 .07ug/ml overnight
(50 ul ea.)
Capture 5dICAM-Ig 17 ng/ml (100ul)
Culture 72 hours, pulse cells last 6 hours

FIG. 5